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Fungal anticancer metabolites: synthesis towards drug discovery

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ABSTRACT: This review summarizes the anticancer potential of fungal metabolites, highlighting the role of total synthesis in sustaining their pharmacological development as an alternative to isolation. This paper also outlines the feasibility of innovative synthetic procedures that facilitate the development of fungal metabolites into drugs that may become a real future perspective. This review demonstrates that total chemical synthesis is a fruitful means of yielding fungal derivatives as aided by recent technological and innovative advancements.

1. Introduction

Fungi are a well-known and valuable source of compounds of therapeutic relevance. They still are a relevant pool from which to search for new lead compounds in the pharmaceutical field. In the past, the drug industry has often centered on libraries of synthetic molecules as it attempts to discover active medical ingredients. However, recent research evolution clearly shows that natural compounds will be ever more important as a hotbed of new drugs in the future, even though the intrinsic complexity of discovering natural product-based drugs requires a deep network of interdisciplinary approaches. Fungi are well-known as a rather unexploited and endless source of novel anticancer compounds. Their structures and mode of action complement the huge amount of active compounds that are extracted from plants. Fungi produce many secondary metabolites with high chemical diversity and are still far from being exhaustively investigated. Notably, the long road that leads to a natural compound becoming a “marketed drug” goes hand in hand with the increasingly challenging necessity for producing higher amounts of compound. These can seldom be obtained through re-isolation from the respective natural tissues. Total organic synthesis is therefore still one of the most efficient alternatives to resupply. Furthermore, natural product total synthesis, in its most essential form, is a so-far unparalleled vehicle for discovery. In fact, thanks to almost unlimited natural diversity, natural compounds are distinguished by their peculiar three-dimensional structures and biological properties, which present incomparable research challenges. Efforts toward the synthesis of target natural compounds have increased knowledge of how to construct molecules and has led to innovative methodologies in enantioselective organic synthesis being developed. This review provides an overview of metabolites isolated from fungi, which exhibit anticancer activity against specific cell lines. This paper also outlines the feasibility of innovative synthetic procedures that allow the development of fungal metabolites into drugs that may become a real future perspective. The literature on metabolites isolated from fungi has recently been updated. In 2014, Nicoletti [1] published a comprehensive overview of fungal secondary metabolites with anticancer activity. He dealt with occurrence, selection, structural diversity and mechanisms. More recently, fungal metabolites with anticancer activity were excellently reviewed by Kiss[2] in 2014 and Kornienko and Evidente in 2015[3]. More specifically, secondary metabolites with anticancer activity isolated from endophytic fungi were reviewed by Zhang in 2011 [4] and by Kharwar and Stierle in 2014.[5] These reviews classified all the compounds according to their chemical structures. These recent and exhaustive publications have been used as a base from which we consider the synthetic feasibility of the most promising compounds, in terms of anticancer properties and drug

development. Furthermore, we extend the scope of our review to those compounds whose synthesis has been realized using unique and challenging synthetic strategies. In line with the aforementioned chemical reviews, compounds are herein classified according to their chemical structure, although some compounds may be included in different chemical classes. The timelines for the selected syntheses are extremely heterogeneous; while synthetic improvements are recent for some of the best-known and widespread compounds, for other classes of compounds, synthetic strategies date back further in time. To our knowledge, this review is the first effort to deal with the total synthesis of these active fungi metabolites. Our goal is to demonstrate that total chemical synthesis is a fruitful means by which to produce natural products and natural product derivatives, not only for those showing simple structures, but even for more complex structures with multiple chiral centers. Due to the massive number of fungal metabolites in existence, the compounds in this review should be seen as a selection of the most representative in terms of application potential. Those not taken into account in this review can be regarded as valuable material for re-evaluation in future publications.

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2. ANTICANCER FUNGAL METABOLITES

2.1 NITROGEN-CONTAINING COMPOUNDS

Alkaloids are a very heterogeneous class of compounds. They are commonly contained in endophytic fungi where they show an important function as a defense against herbivores and insects. It is worth noting that some of the most important anticancer plant alkaloids have been isolated from endophytic fungi. The chemical structures of the alkaloids described in this review are reported in Figure 1.

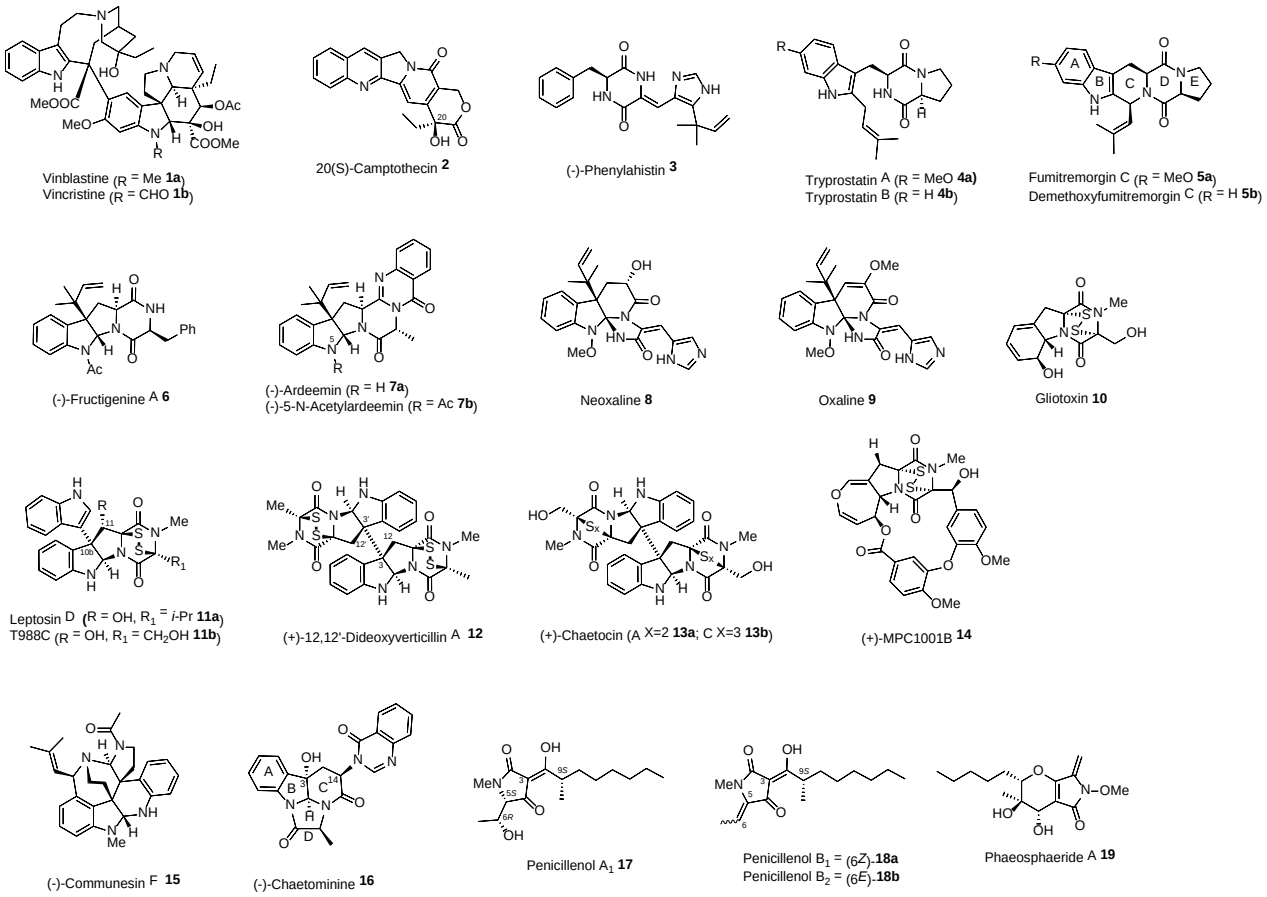


Figure 1 *Structures of the nitrogen-containing compounds discussed*

When discussing fungal anticancer metabolites, we cannot help but cite Vinblastine (**1a** Figure 1) and Vincristine (**1b**), which are the most widely known constituents of the *Vinca* alkaloid class, and Camptothecin (CPT **2**, Figure 1).

First introduced into the clinic over 50 years ago, **1a** and **1b** have provided one of the most important contributions that natural products have given to chemotherapy and are still nowadays efficacious clinical drugs used for the treatment of a wide range of cancerous diseases.[6] Originally isolated from *Catharanthus roseus*, they have also been found to be produced by some endophytic strains of *Alternaria* sp. and *Fusarium oxysporum*.[1] However, the main source of Vinca alkaloids is still plants, as a consequence an inclusive discussion of the most recent progresses in the synthesis of **1a** and **1b** is out of scope of our overview. For very recent updates on the subject, please see Boger and Thomas' reviews.[6-7]

Camptothecin is a pentacyclic quinoline alkaloid that was initially isolated, in 1966 by Wall and co-workers [8], from the wood of *Camptotheca acuminata* (Nyssaceae), a plant native to Tibet and China (called 'xi shu' or 'happy tree'). Historically, it has been widely-known for its therapeutic properties. In 2005, the compound was also isolated from an endophytic fungus *Entrophospora infrequens* that is found in an antitumor plant *Nothapodytes foetida* in the Western coast of India.[9] Initial human clinical studies were complicated by CPT's poor solubility in water, high toxicity and rapid inactivation, caused by E ring hydrolysis under physiological conditions, that restrict its therapeutic applications. Interest in CPT was renewed by the discovery of its peculiar property of inhibiting DNA topoisomerase I [10] leading to numerous CPT derivatives being synthesized in an attempt to obtain more soluble and stable compounds over the last 2 decades. This effort yielded two semi-synthetic CPT analogues that have been clinically approved by the FDA, namely Irinotecan (sold by Pfizer as Camptosar®, against metastatic colorectal carcinoma) and Topotecan (produced by GlaxoSmith-Kline as Hycamtin®, for the treatment of ovarian and small-cell lung cancer).

An exhaustive dissertation on the syntheses of CPT and its derivatives lies outside the focus of this review as CPT is a typical plant metabolite presumably isolated by fungi because of horizontal gene transfer. However, research studies into camptothecin total synthesis, structure–activity relationship, mechanism of action, pharmacology, pre-clinical studies and clinic trials have recently been widely discussed in several excellent reviews.[11]

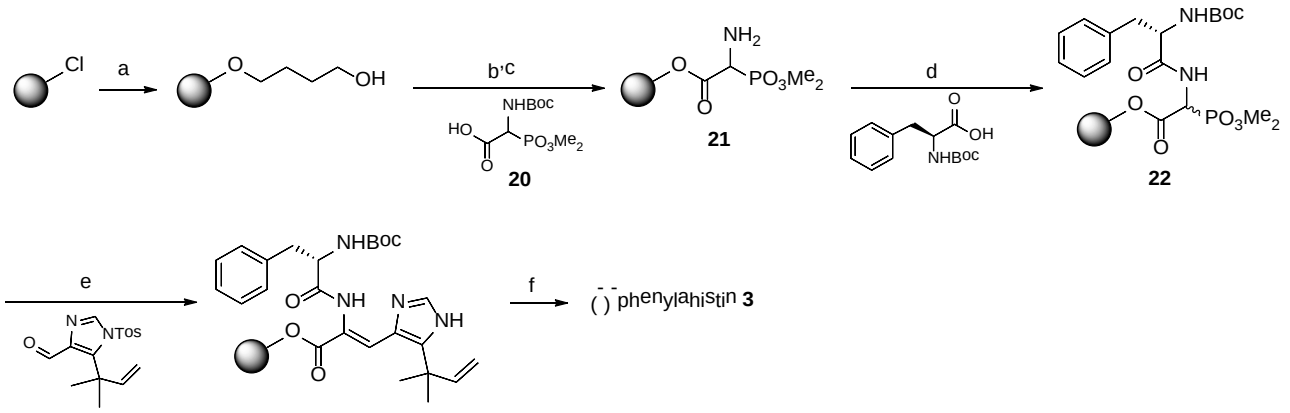
2.1.1 *Phenylahistin (3)*

2,5-Diketopiperazines (DKPs **3**-**6** Figure 1) present a typical six-membered heterocyclic ring containing two nitrogen atoms in opposite positions (C1,C4), which is usually biosynthesized through the condensation of two α-amino acids. DKPs have been isolated from Aspergillus and Penicillium species and are characterized by a wide range of bioactivity and have proven themselves to be important sources for drug development.[12]

(-)-Phenylahistin (**3** Figure 1) and related derivatives have exhibited strong growth inhibition in various tumor cell lines because of their strong binding affinity for microtubules.[3, 13] [14] [15] It was isolated from *Aspergillus ustus* as a racemic mixture by Kanoh *et al.* in 1997. [16] Its chemical structure includes an *L*-phenylalanine and a (*Z*)-isoprenylated dehydrohistidine residue with a quaternary carbon at the 5-position of the imidazole ring. The more potent enantiomer (-)-phenylahistine acts at the colchicine binding site on tubulin and exhibits cytotoxic activity against a wide range of tumor cell lines in both *in vitro* and *in vivo* tests.[3, 13] Its semisynthetic analogue, Plinabulin (NPI-2358), is progressing to phase 3 trials on patients with non-small cell lung cancer (NSCLC).[12] An interesting structure−activity relationship study of phenylahistine derivative antimicrotubule agents was reported in 2012 by Yamazaki and co-workers.[17] However, the total syntheses of natural (-)-phenylahistine is a useful tool with which to shed light on its biological activity and to aid the design of new diketopiperazine-structure-based anticancer drugs.

In 2000, Hayashi *et al.* achieved the total synthesis of (-)-phenylahistin in which the key steps were the formation of the isoprenylated imidazole from ethyl isobutyrate and its condensation with the diketopiperazine derivative.[14] The total yield of the final enantiopure (-)-**3** was unfortunately very low (1%).

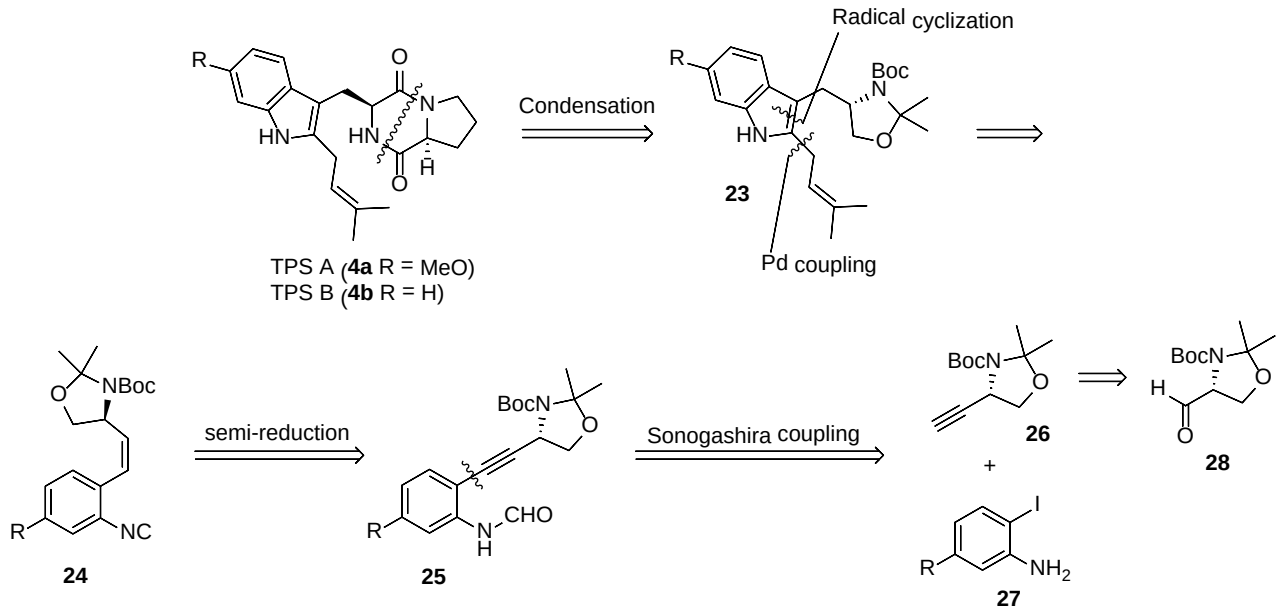
Two research groups later developed an alternative synthetic pathway to the dehydroamino acid moiety using a Horner–Emmons type coupling between a phosphinyl glycine ester and a formylimidazole as the key step.[18] In 2005, Couladouros and Magos prepared (-)-phenylahistine in high yields (47% overall for four steps) and high optical purity using this approach.[18a] Their efforts were especially aimed at seeking synthetic approaches that are amenable to solid-phase application and led to the development of the unique solid-phase total synthesis of (-)-phenylahistin, which was based on the Horner–Emmons reaction (Scheme 1).[18b] Extended Merrifield resin was coupled with known acid **20** to give the key solid supported glycine phosphonate **21**, whose coupling was performed with the *N*-protected L-amino acid Boc-L-Phe-OH. The mild Horner–Emmons conditions were applied to resin **22** to load the imidazole moiety. This methodology is a useful tool for the solid-phase synthesis of dehydro-2,5-diketopiperazines as it enables the rapid parallel synthesis of a large number of diversified structures.



Scheme 1 *Couladouros and Magos' solid-phase synthesis of (-)-phenylahistin*: a) Merrifield resin, 1,4-butanediol, NaH, imidazole, Bu_4NI, DMF; b) DCC, DMAP, DCM/DMF; c) (+)-CSA, DCM; d) HOBt, EDC·HCl, Et_3N, DCM; e) DBU, DCM; f) (+)-CSA, DCM then Et_3N, DCM

2.1.2 *Tryprostatin A (4a) and B (4b)*

In 1995, Osada's group reported the isolation of Tryprostatin (TPS) A and B (**4a** and **4b** Figure 1) from a marine strain (BM 939) of *Aspergillus fumigatus*. The TPS dikepiperazine scaffold derives from tryptophan and proline with a prenylated indole moiety. Both natural compounds are cell cycle inhibitors at the G2/M phase barrier with TPS B being more potent than A. Furthermore, TPS A was found to be an inhibitor of the breast cancer resistance protein.[19] [20] Most of the TPS A and B syntheses published before 2005 have been reviewed by Maison.[21] We herein update the recent developments in the total syntheses of TPS A and B. Recent syntheses of TPS analogues were reported by Stanovnik *et al.* and De Kimpe *at al.* in 2008 and 2013, respectively.[20, 22] A useful SAR study into the cell cycle inhibitory effects of TPS analogues and their potential antitumor antimitotic agents has been carried out by Cook *et al*.[23], who also accomplished the synthesis of TPS A and B enantiomers and diastereomers using already-known methods.[23] In 2000, Lobo and co-workers applied the pericyclic aza-Cope reaction to the asymmetric synthesis of TPS B for the first time. Full details of this work, which involved an acid-catalyzed rearrangement of an appropriately substituted tryptophan, were described in 2006 by the same research group.[24] Fukuyama's group has developed three different syntheses for the 2-prenyl tryptophan core of tryprostatins along with their total syntheses,[25] but only the one we report in Scheme 2 is worthy of attention.[25-26] The key step in this strategy is the selective radical-mediated cyclization of isocyanide **24** that, along with a palladium-mediated coupling with a prenyl-group donor, lead to the facile construction of the di-substituted indole core **23**. Isocyanide **24** was obtained from alkyne **25**, which in turn was synthetized via the Sonogashira coupling of the terminal alkyne **26** with the aromatic iodide **27**. In order for the final molecule to be obtained in high enantiomeric purity, alkyne **26** which was derived from Garner's aldehyde **28**, was used as a latent amino acid unit to be included in the diketopiperazine skeleton. TPS B was synthesized in 11 steps (from **28**) in a 33% overall yield and TPS A in a 30% overall yield using this approach (from **26** both on a half-gram scale). Unfortunately, this procedure is not eco-friendly and it is rather unsuitable for the industrial production of potential drugs as it involves toxic stannyl derivatives in the radical-mediated indole synthesis and uses highly toxic triphosgene as a reagent to obtain isocyanide **24**.

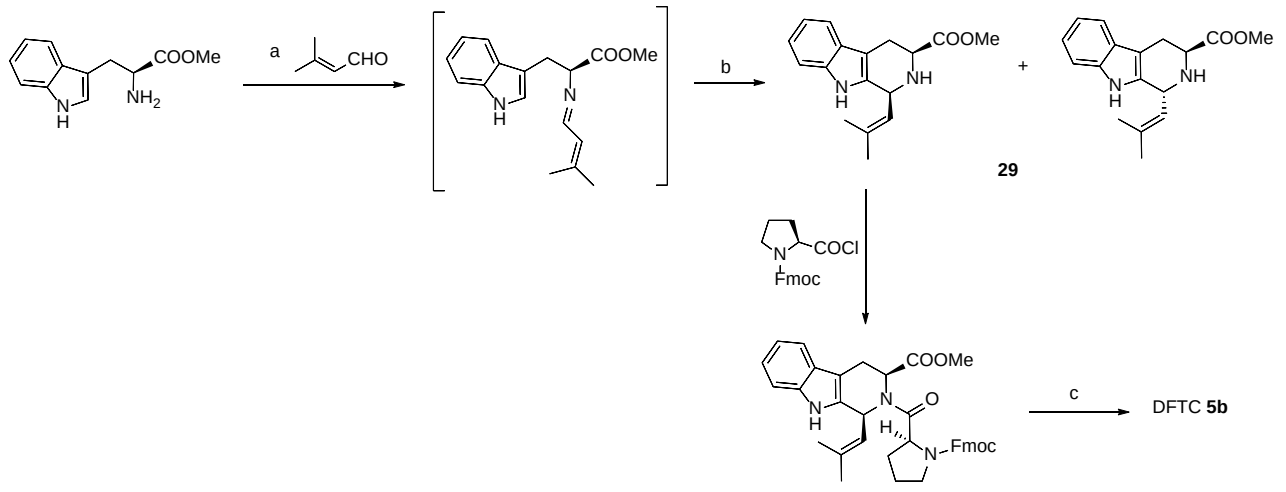


Scheme 2 *Fukuyama's group strategy for the synthesis of TPS A and B.*

2.1.3 *Fumitremorgin C (5a) and Demethoxyfumitremorgin C (5b)*

Together with TPS A and B, Osada's group identified plausible biogenetic derivatives fumitremorgin C (FTC **5a** Figure 1) and demethoxyfumitremorgin C (DFTC **5b**) from the fermentation broth *of Aspergillus fumigatus* BM939.[27] They have recently been isolated from *Aspergillus sydowi*.[28] Both FTC and DFTC have proved to be inhibitors of mammalian cell cycle, like TPS A and B.[27]

A complete review of the synthesis of Fumitremorgins was presented by Hino and Nagakawa in 1997.[27a] One of the most straightforward ways to build FTC and DFTC key intermediates, **29**, makes use of the Pictet–Spengler reaction that involves the acid-catalyzed intramolecular condensation of an iminium ion and an aromatic C-nucleophile. After 1997, Ganesan [27b, 29] and Bailey [30] devised new total syntheses of DFTC and FTC, respectively, exploiting this approach. Nevertheless, Ganesan's procedure led to a mixture of diastereomers. By contrast, Bailey *et al.* managed to develop a diastereoselective three-step synthesis of enantiopure DFTC in a 21% overall yield (Scheme 3). His route furnished tetrahydro-β-carboline derivative **29** with 6:1 *cis* selectivity.



Scheme 3 *Bailey's synthesis of enantiopure DFTC*: a) 3Å molecular sieves; b) $CHCl_3$, TFA (38%); c) Piperidine, DMF (58%).

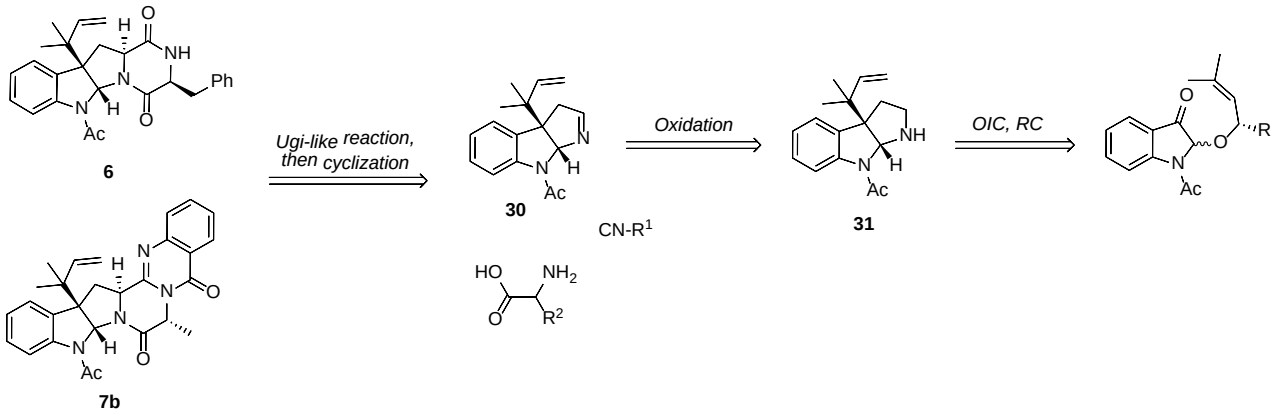
Later, in 2012, Jia and co-workers [31] applied a new $Mg(ClO_4)_2$-catalyzed intramolecular allylic amination reaction to give the tetrahydro-β-carboline skeleton in a 1:1 *cis*:*trans* ratio and then finished the total synthesis of DFTC from the *cis*-isomer. Enantiopure DFTC was obtained in a 24% overall yield in six steps, starting from *N*-Boc protected tryptophan.

2.1.4 *Fructigenin A (6), Ardeemin (7a) and N-Acetylardeemin (7b)*

(-)-fructigenine A (**6** Figure 1**)** contains both a 2,5-diketopiperazine ring and a 3-substituted hexahydropyrrolo[2,3-*b*]indole. This framework bears a 1,1-dimethylallyl ("reverse-prenyl") group and is a widely distributed structural unit featuring several biologically active alkaloids, such as (-)-ardeemin and 5-*N*-acetylardeemin (**7a** and **7b** Figure 1). (-)-Fructigenine A were isolated from *Penicillium fructigenium* by Kunizo *et al.* and showed growth-inhibitory activity against leukemia L-5178Y cells.[32] Ardeemins **7** were isolated from *Aspergillus fischerii* by McAlpine and co-workers [33] and demonstrated a potent ability to reverse multi-drug resistance (MDR).[34] *N*-acetylardeemin, in particular, is one of the most potent known inhibitors of MDR to antitumor agents, such as vinblastine and taxol.[34]

Recent advances in the synthesis of enantiopure (-)-ardeemin have already been cited in Yong Qin *et al.* (2009)[34] and also reported in Alvarez group's review (2011).[35]

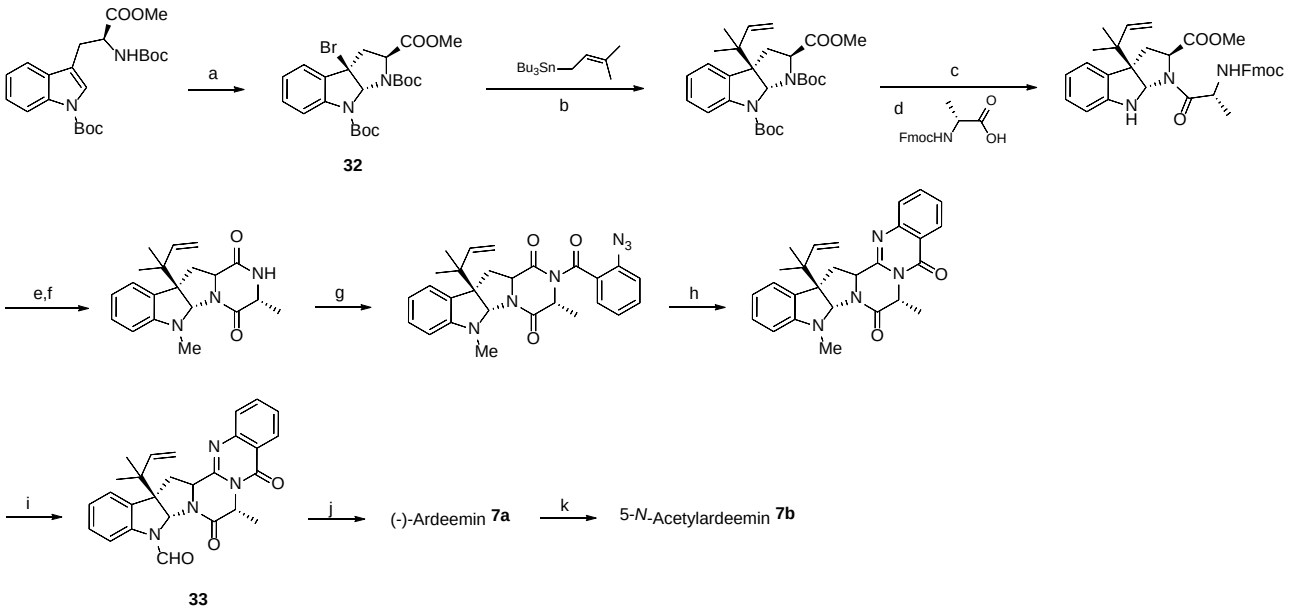
In 2010, Kawasaki *et al.* managed to achieve the first asymmetric total synthesis of **6** and a new synthetic pathway for **7b** via an imine derivative **30** (Scheme 4).[36] The synthetic route involves an Ugi three-component reaction of **30** with the corresponding amino acid and isonitrile followed by cyclization to construct the pyrazino ring. The pyrroloindoline imine **30** is obtained via the regioselective oxidation of enantiomerically enriched pyrroloindoline **31**, which is readily prepared by an asymmetric olefination/isomerization/Claisen rearrangement (OIC) and reductive cyclization (RC). (-)-Fructigenine A was obtained in four steps and in a 45% overall yield from imine **30**. (-)-5-*N*-acetylardeemin was achieved in a 37.6% three-step yield from the same common intermediate which, in turn, was produced after ten steps and in a 26.5% overall yield with high enantiomeric purity (99% ee).



Scheme 4 *Kawasaki's approach for synthetizing enantiopure **6** and **7b***

A new total synthesis of (-)-ardeemin and (-)-acetylardeemin was published by Qin's group in 2012 (Scheme 5).[37] The key step was a silver-promoted Friedel-Crafts reation to achieve the direct isoprenylation of bromopyrroloindoline **32** with prenyl tributylstannane. (-)-Formylardeemin **33** was obtained from **32** in a 36% overall yield in 8 steps. **7a** was readily prepared from **33** via simple deformylation and **7b** was prepared from **7a** by a single step of acetylation. The

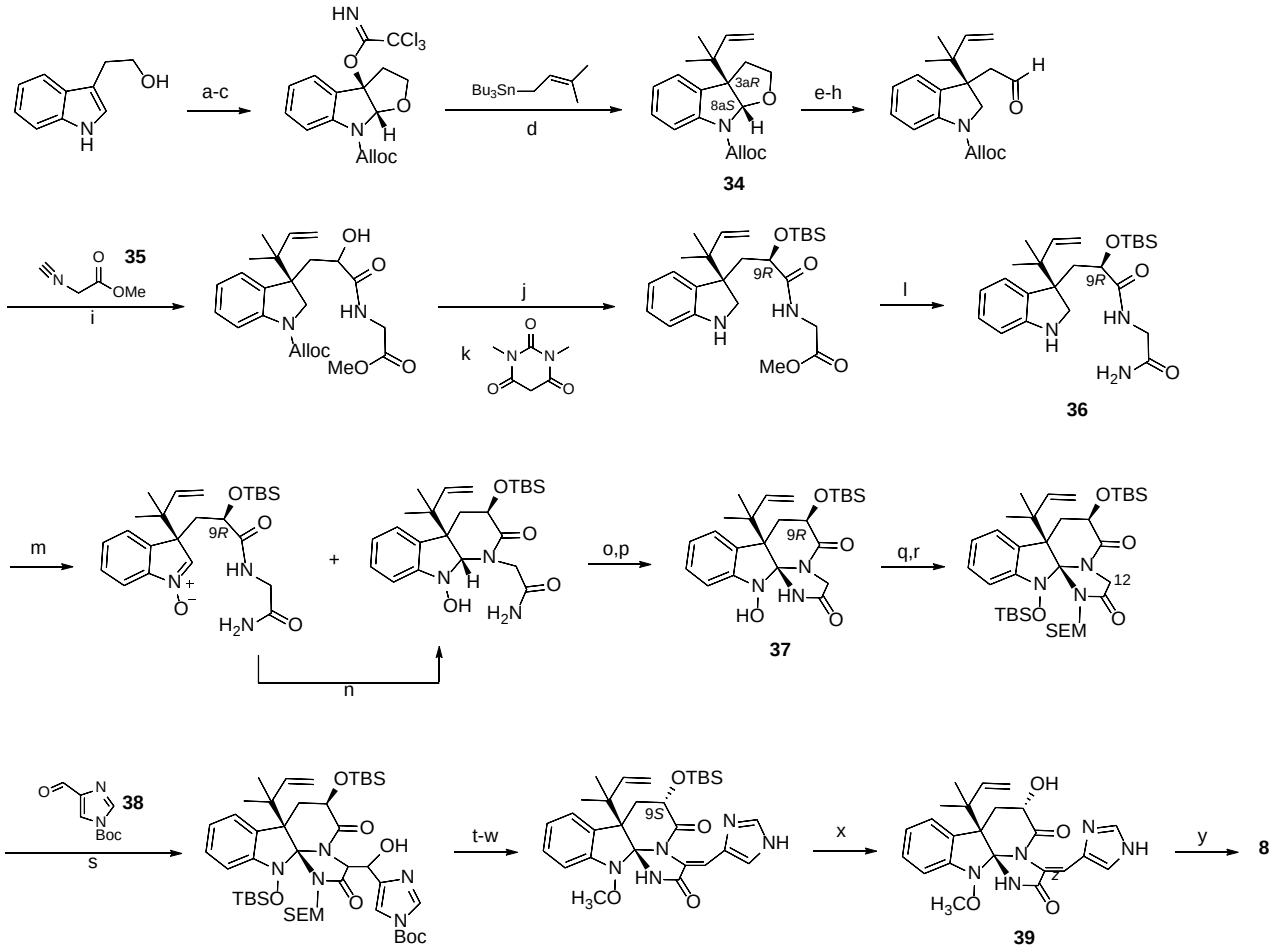
highly efficient installation of the isoprenyl group on the pyrroloindoline skeleton greatly enhanced synthetic efficiency and made the whole procedure a practical tool for the large-scale synthesis of **7a** and **7b**, except for the fact that it includes the use of a toxic stannane.



Scheme 5 *Qin's group synthesis of **7a** and **7b***: a) NBS, ref. 45 and ref. therein (86%); b) $AgClO_4$, Cs_2CO_3 (81-93%); c) TMSI, MeCN, (90%); d) HATU, Et_3N, DMF (80%); e) 37% aqueous HCHO, $NaBH_3CN$, MeCN–AcOH (90%); f) Et_2NH, THF (93%); g) BuLi, *o*-azidobenzoic anhydride, THF (92%); h) Bu_3P, toluene (86%); i) PDC, silica gel, DCM (80%); j) 8% aqueous NaOH in MeOH (85%); ref. 37 and ref. therein.

2.1.5 *Neoxaline (8) and Oxaline (9)*

Neoxaline (**8** Figure 1) and structurally related oxaline (**9**) are biologically active prenylated indole alkaloids that bear an indoline spiroaminal structure with a "reverse prenyl" group and a (*E*)-dehydrohistidine moiety (Figure 1).[38] Oxaline families were isolated from *Penicillium spp.* and found to exhibit moderate antibacterial, antifungal and anticancer activities.[38] Ōmura and co-workers isolated Neoxaline from a culture broth of *Aspergillus japonicas* in 1979.[38] Neoxaline was found to inhibit cell proliferation and arrest cell cycles during the M phase. Both **8** and **9** were found to be inhibitors of tubulin polymerization.[38a] Only Ōmura and co-workers have successfully carried out the total synthesis of neoxaline family alkaloids. They initially established neoxaline as their synthetic target and reported the construction of the indoline spiroaminal framework in 2005.[38a] Afterwards, but only in 2013, did they manage to accomplish the first asymmetric total synthesis of **8** (Scheme 6) and the determination of its absolute configuration.[38b] Pivotal steps in the synthesis were: *i)* the stereoselective introduction of the reverse prenyl group at the benzylic ring junction via treatment with prenyl tributylstannane to give (3a*R*,8a*S*)-**34** as a single diastereomer; *ii)* the preparation of cyclization precursor **36**, involving the boric acid-mediated addition of isocyanoacetate **35**; *iii)* the construction of indoline spiroaminal (9*R*)-**37** via three oxidations and two cyclizations from indoline **36**; *iv)* the insertion of the conjugated imidazole at C12 using an aldol reaction of imidazolyl aldehyde **38**; *v)* the final photoisomerization of unnatural (*Z*)-neoxaline **39** using mercury lamp irradiation to obtain natural (*E*)-neoxaline.



Scheme 6 *Ōmura's first asymmetric total synthesis of* ***8***: a) *t*-BuOOH, (+)-DITP, $Ti(O\text{-}i\text{-}Pr)_4$, DCM (99%, 99% ee); b) Alloc-Cl, $NaHCO_3$, DCM, H_2O (94%); c) Cl_3CCN, DBU, DCM (quant.); d) $BF_3{\cdot}OEt_2$, DCM (87%); e) $Pd(PPh_3)_4$, dimedone, MeOH (98%); f) $NaBH(OAc)_3$, AcOH, DCE (88%); g) Alloc-Cl, $NaHCO_3$, DCM, H_2O (97%); h) Dess Martin periodinane, DCM (quant.); i) $B(OH)_3$, DMF (91%); j) TBSOTf, 2,6-lutidine, DCM (quant.); k) $Pd(PPh_3)_4$, THF (83%); l) 2M NH_3 in MeOH (99%); m) $Na_2WO_4{\cdot}2H_2O$, $H_2O_2{\cdot}$urea, MeOH, H_2O; n) Et_3N, benzene (93%, two steps); o) $Pb(OAc)_4$, DCM (96%); p) TBAOH, DCM (93%); q) TBSOTf, DIPEA, DCM (98%); r) SEMCl, NaH, THF (97%); s) LiHMDS, THF (59%); t) EDC, $CuCl_2$, toluene (76%); u) TBAF, THF (88%); v) MeI, K_2CO_3, DMF (86%); w) Me_3Al, DCM (71%); x) HF·pyridine (73%); y) hν (λ < 325 nm), MeOH (55%).

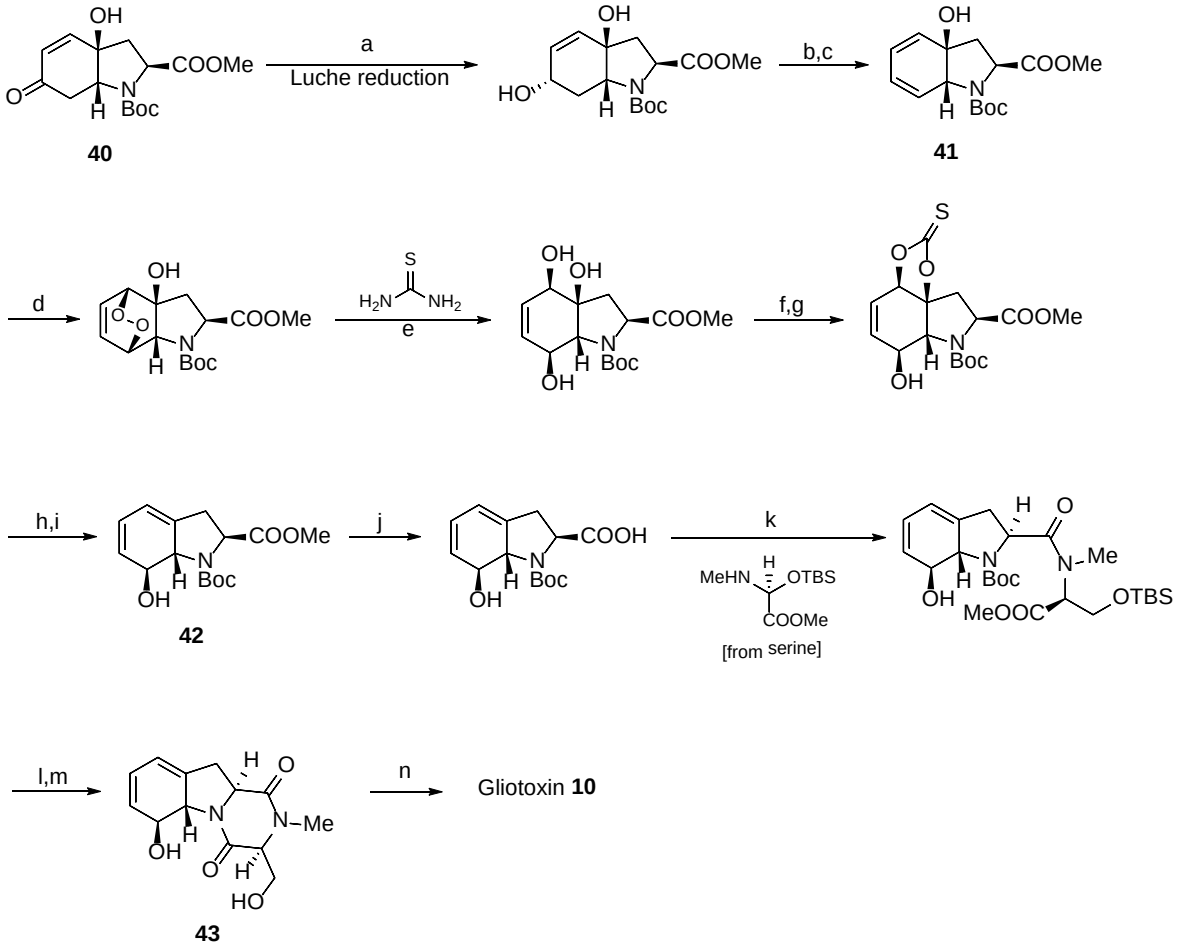
In 2015, Ōmura's group published an improved asymmetric total synthesis of **8**, in which was accomplished the direct stereoselective construction of (*E*)-dehydrohistidine.[38c] This new synthesis of neoxaline led the overall yield to 7.9% yield in 24 steps and allowed more than 300 mg of final product to be prepared. In the same article, the first total synthesis of oxaline was also described, although it was via a slightly modified synthetic route.[38c]

2.1.6 *Gliotoxin (10)*

Epipolythiodioxopiperazines (ETPs, **10**-**14** Figure 1) have attracted considerable attention thanks to their potent anticancer activity. They are fungal metabolites that possess peculiar architectures with a polysulfide bridge onto a diketopiperazine six membered ring. They can present a monomeric (**10**, **11** and **14** Figure 1) or a dimeric scaffold (**12** and **13** Figure 1) and are characterized by great activities against parasites, viruses, bacteria and cancer cells.[39] For a brief collection of the methods for the building of the polysulfide bridges of ETPs, see ref. 40 and references therein.[40]

Gliotoxin (**10** Figure 1), which is produced by various species of *Gladiocladium*, *Trichoderma*, *Aspergillus* and *Penicillium*, [1, 41] belongs to the ETPs class as it is based on tryptophan and a single dithiodioxopiperazine moiety. In the 1970s, Kishi's group managed to accomplish the first total synthesis of **10 by** masking the 3,6-dithiodiketopiperazine core with anisaldehyde and then generating the desired epidithiodiketopiperazine at a later stage. [41]

Since then no great effort had been made to carry out the enantioselective synthesis of this compound, until 2012 when Nicolaou and co-workers obtained enantiopure gliotoxin. Nicolaou's strategy passed through bicyclic hydroxy diene **42** which was obtained in multigram quantities from tyrosine-derived **40** (Scheme 7). The nine-step sequence is noteworthy for its use of the [4+2] photooxygenation of diene **41** to generate a hydroxyl endoperoxide. **10** was then prepared from **42** via five synthetic steps, involving the crucial final sulfenylation of **43**, which was based on the use of LiHMDS and elemental sulfur in THF at 25°C. A sulfenylation step also furnished gliotoxin G as a side product in a 33% yield. In the end, Nicolaou's synthesis furnished **10** with in an overall yield of around 7%.

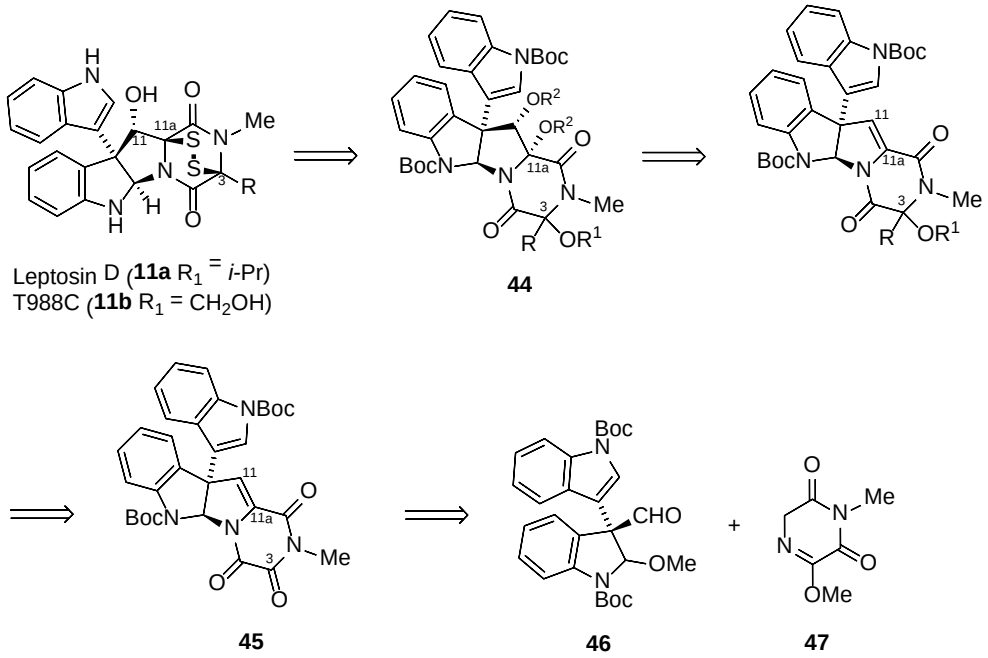


Scheme 7 *Nicolaou's asymmetric synthesis of **10***: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (99%); b) Ac_2O, Et_3N, 4-DMAP, DCM (91%); c) $Pd(OAc)_2$, PPh_3, Et_3N, toluene (86%); d) O_2, TPP, hν, DCM (73%); e) MeOH (84%); f) TIPSOTf, Et_3N, DCM (96%); g) $(im)_2C=S$, toluene (90%); h) $P(OMe)_3$ (82%); i) HCl, DCM/Et_2O (98%); j) aq LiOH /THF (99%); k) HOAt, HATU, DIPEA, DCM (88%); l) TFA/DCM; m) Et_3N/THF (63% two steps); n) LiHMDS 1.0 M in THF, S_8 then LiHMDS (23%).

2.1.7 *Leptosin D (11a) and T988C (11b)*

Many ETP toxins possess a hydroxyl substituent at C11 of the pyrrolidine ring and a C10b quaternary stereo center. Leptosin D and T988C (**11a** and **11b**, Figure 1) belong to this group and Overman and co-workers developed a common

strategy for preparing both of them in 2013.[39a] Central to their synthetic strategy (Scheme 8) was the α-ketoimide carbonyl and alkylidene double bond unit of Boc-gliocladin **45**, prepared via the convergent gram-scale coupling of enantioenriched pro-dielectrophile **46** with pro-dinucleophile isatin **47**. Further crucial steps in the total syntheses were: *i)* the introduction of C3 substituents via the chemoselective addition of an appropriate organometallic reagent to the C3 carbonyl group of **45**; *ii)* the stereoselective dihydroxylation of the C11−C11a double bond; *iii)* the stereoselective construction of the disulfide bridge via the BF_3•OEt_2-promoted reaction of H_2S with the displacement of the oxygen substituents (acetoxy or siloxy) at C3 and C11a of precursor **44**. The (+)-**45** intermediate was obtained from **47** via a ten-step route with a 15% overall yield. Moreover, the divergent sequences developed in Overman's work for preparing the target ETP compounds (6−9 steps, 14−33% yield) supplied plentiful quantities of **11a** and **11b**, which were used for *in vitro* cytotoxicity evaluations which demonstrated that the disulfide motif was required for the activity of these ETPs.[39a]



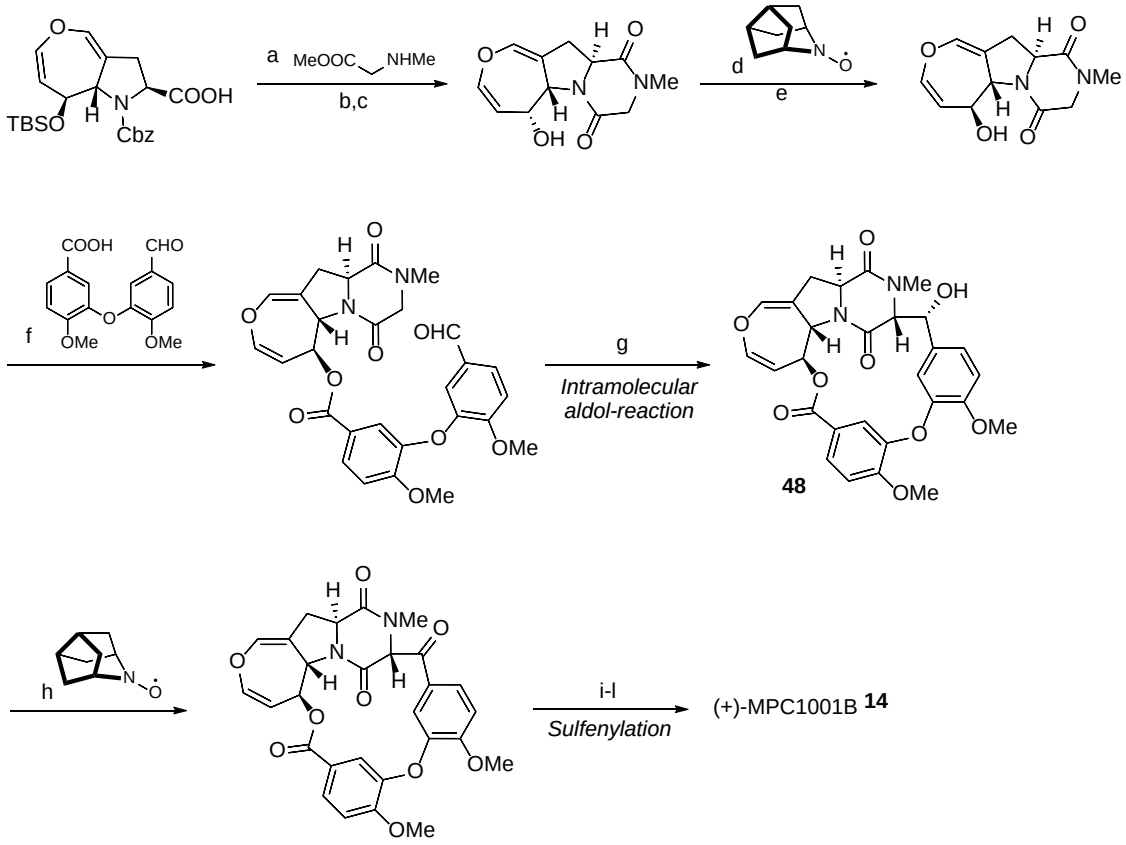
Scheme 8 *Overman's strategy for the first asymmetric synthesis of Leptosin D **11a** and T988C **11b***

Moving to dimeric ETP natural alkaloids, (+)-12,12´-dideoxyverticillin A (**12**, Figure 1) and (+)-chaetocins (**13**, Figure 1) have been the most intensely investigated. Movassaghi's ground breaking study on the biogenetically inspired syntheses of these compounds is a remarkable central intellectual construct toward the development of new syntheses for dimeric ETPs.[39c, 42] Highly cytotoxic **12** and **13** were isolated from marine *Penicillium sp.* [43] and the fungi of the *Chaetomium* genus [44], respectively. Since 2009, when Movassaghi and Kim published their pioneering total synthesis of **12** in *Science*, several enantioselective total syntheses of dimeric ETPs have been accomplished [39a] In this case, one more difficulty arises from the dimeric structure connected with a chiral quaternary carbon. As Movassaghi's work on **12**, including his enantioselective synthesis of (+)-Chaetocins A **13a** and B **13b**, has already been widely reviewed,[39c, 42, 45] we only wish to bring a few points to mind in this review. In 2009, Movassaghi [43] reported the first total synthesis of (+)-12,12´-dideoxyverticillin A **12** and Sodeoka [44a] accomplished the total synthesis of (+)-chaetocin A **13a** in 2010. They both used 3,6-dihydroxyDKP and H_2S to construct the ETP motif. Later in 2010, Movassaghi's group described the use of potassium trithiocarbonate (K_2CS_3) to generate an ETP moiety from a monosilylated 3,6-dihydroxyDKP intermediate in order to obtain **12** and **13**.[44b] Moreover, Movassaghi performed the

key dimerization step by making use of cobalt-base chemistry and developing an effective multigram scale synthesis to simultaneously join the two vicinal C3 and C3' quaternary stereocenters.[39c, 42] This synthetic shrewdness led to a high level of stereochemical control and chemoselectivity in the sulfidation of dimeric ETP intermediates.

2.1.8 *(+)-MPC1001B (14)*

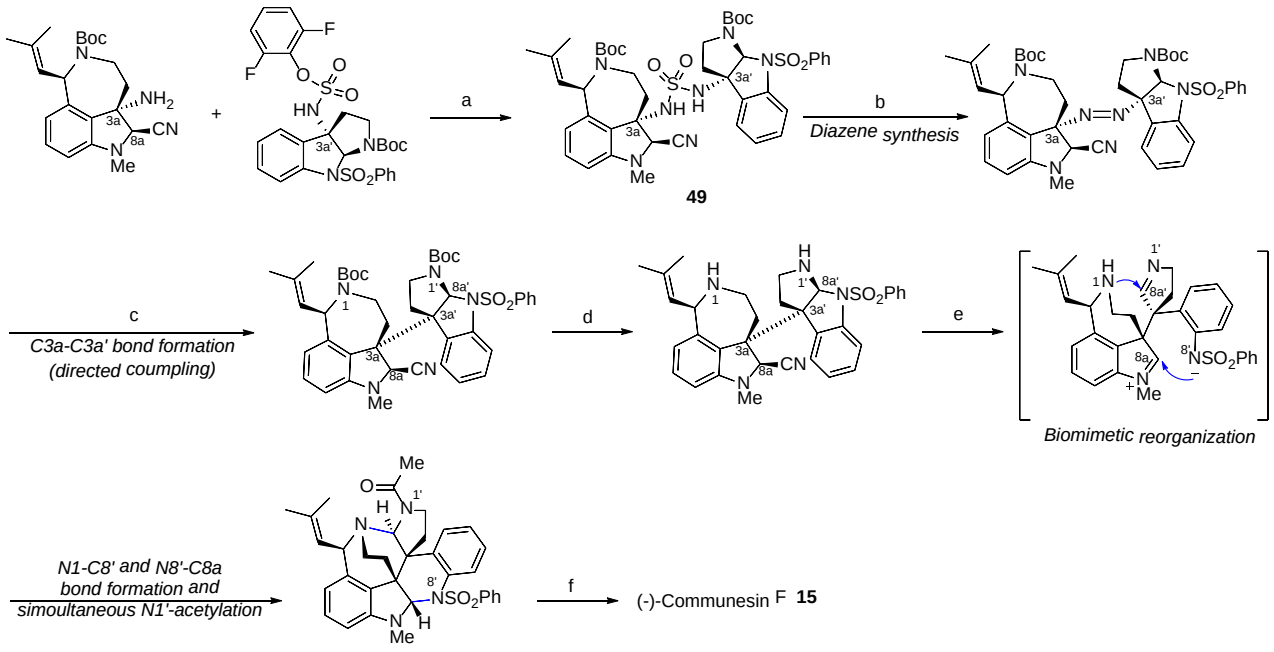
Fungal metabolites, called MPC1001, isolated from a strain of *Cladorrhinum sp*. [1], display a wide range of anticancer activities, such as antiproliferative and apoptosis-inducing activity toward colon and prostate cancer cell lines.[46] These ETPs are characterized by a unique seven-member dihydrooxepine and a characteristic 15-membered ring which make their production achievement very difficult. Tokuyama group's total synthesis of (+)-MPC1001B (**14** Figure 1), published in 2016 for the first time, therefore deserves to be mentioned.[46b] The conceived synthetic pathway is summarized in Scheme 9. Macrocycle **48** was built by exploiting an intramolecular aldol reaction to form the C3-C7" bond and two consecutive acyl condensations. The final synthetic step was sulfenylation accomplished via stepwise trityl trisulfide (TrSSS)-group transfer. The overall yield was only about 3% for 14 steps because of the multistep sulfenylation, which did not prove to be very efficient.



Scheme 9 *Tokuyama's synthesis of (+)-MPC1001B*: a) BOP-Cl, Et_3N, DCM (95%); b) Et_3SiH, cat. $Pd(OAc)_2$, cat.Et_3N, DCM (94%); c) TBAF, THF (97%); d) cat. nor-AZADO, $PhI(OAc)_2$, DCM (86%); e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, DCM/EtOH, (93%); f) WSCD, cat. DMAP, DCM (quant); g) TBAF, THF (71%); h) cat. AZADO, $PhI(OAc)_2$, DCM, pH 7.4 phosphate buffer (79%); i) LiHMDS, TrSSSCl, THF three consecutive treatments (overall 22%); j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, DCM/EtOH, (quant); k) $HSCH_2CH_2SO_3Na$, cat. DIPEA, DMF/H_2O, RT; l) O_2, AcOEt/MeOH (33% two steps).

2.1.9 *(-)-Communesin F (15)*

Communesins are a motley family of alkaloids derived from various marine and terrestrial *Penicillium* fungi that possess antiproliferative activity and significant cytotoxicity against lymphocytic leukemia.[47] Recent advances in the total synthesis of this class of compounds have been fully and deeply examined by Trost [47a] and Ma *et al.* [47b] in their accounts, both published in 2015. Herein, we simply wish to highlight the very latest progress in this field, which is well represented by the first convergent and biomimetic synthesis of (-)-communesin F (**15** Figure 1) reported by Movassaghi *et al.* in 2016.[48] The core of the whole synthesis strategy (Scheme 10) is made up of: *i)* an expedient diazene-based assembly for directed advanced fragments linkage to sew the C3a−C3a' bond leading to complex sulfamide **49**, in three steps on a gram scale; *ii)* the subsequent guided biomimetic aminal rearrangement that selectively yielded the heptacyclic communesin core in only three additional steps. Both the versatile syntheses of the two initial fragments [48], their stereo-controlled assembly and the final acylation of the communesin core have succeeded in providing a unified synthetic tool for the construction of structurally related complex alkaloids.

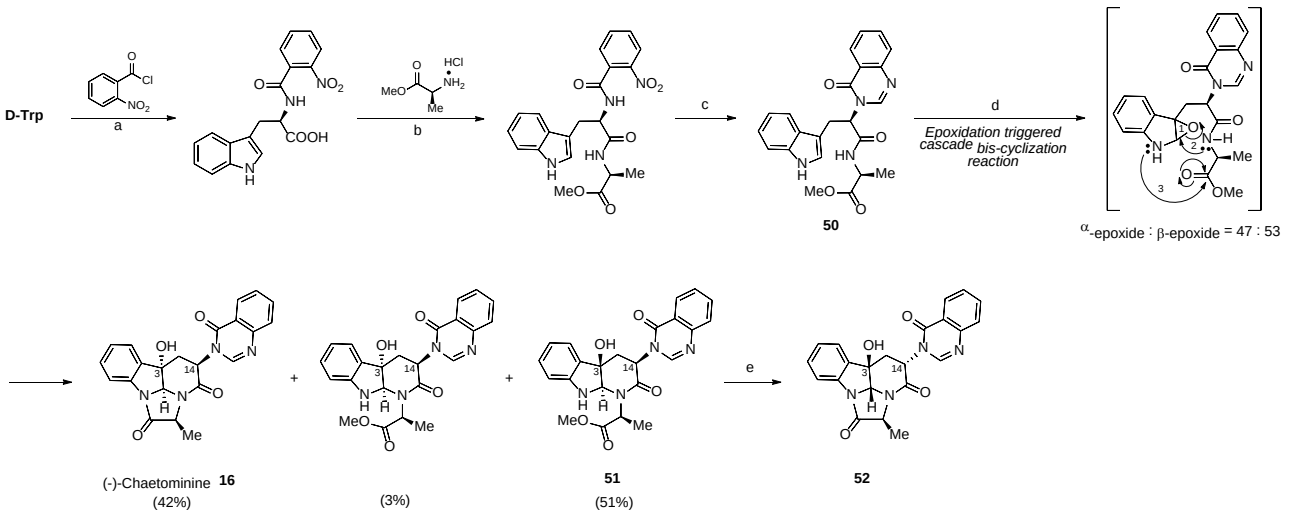


Scheme 10 *Key steps in Movassaghi's biomimetic strategy for synthetizing (-)-Communesin F* ***15***: a) 4-(*N*,*N*-dimethylamino)pyridine, THF (80%); b) polystyrene-2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, N-chloro-N-methylbenzamide, MeOH (57%); c) hν (350 nm) (39%); d) $Sc(OTf)_3$, F_3CCH_2OH (67%); e) *t*-BuOLi, MeOH; dry PPTS, Ac_2O (82%; f) Na(Hg), NaH_2PO_4, THF, MeOH (83%).

2.1.10 *(-)-Chaetominine (16)*

Ten years ago, in 2006, (-)-chaetominine (**16** Figure 1) was isolated by Tan *et al.* from a solid-substrate culture of *Chaetomium sp.* IFB-E015 [49], an endophytic fungus on *Adenophora axilliflora* leaves, and from the metabolites of *Aspergillus sp.* HT-2.[50] It has exhibited potent cytotoxicity against human leukemia K562 and colon cancer cell SW1116 lines.[49] **16** is a modified tripeptide alkaloid which derives from Tryptophan, L-alanine, anthranilic acid and formic acid. Its peculiar structure is characterized by a tetracyclic core, containing four stereocenters and a quinazolinone segment. Owing to this fascinating architecture and its potential biological profiles, a great deal of synthetic effort has been focused on its total synthesis. Soon after its isolation, in 2007, a first total of **16** was published. For a concise case history on the enantioselective syntheses of (-)-chaetominine, from then to 2009, see reference 51 [51] and the papers cited therein. In this review, we focus our attention on the new and shorter syntheses reported by

Huang and coworkers in 2014.[51a, 52] In their first paper, they disclosed the absolute shortest synthesis to date with the highest overall yield [52a] where **16** is achieved in four steps with an overall yield of 33.4% from D-tryptophan (Scheme 11). Pivotal features of this bio-inspired strategy involve: *i)* the use of a nitro group as a latent amino group for the one-pot construction of the quinazolinone system; *ii)* a one-pot transformation of intermediate **50** through a cascade indole epoxidation - amidative cyclization - lactamization reaction sequence to ensure C/D ring closure. Although the yield of **16** from **50** is modest, the strategy is highly efficient (three one-pot reaction) and also avoids the use of protecting groups. C3/C14 *syn*-selection occurs during the cascade sequence but *β*-epoxide is predominately formed followed by the base-promoted epimerization at C14 of compound **51** to compound **52**. Taking advantage of these results, still in 2014, Huang *et al.* managed to accomplish an unprecedented bio-mimetic total synthesis of **16** from the suggested biosynthetic parent L-tryptophan.[51a] They thus proved that L-tryptophan, *o*-nitrobenzoyl chloride, L-alanine and anthranilic acid can be assembled in five steps to give **16** in an overall yield of 23.2%. Based on these findings, a plausible biosynthetic pathway for **16** was then suggested [52b] and a comprehensive investigation was carried out to clarify the stereochemical requirements for the double cyclization and clarify the physical and chemical properties of **16**.[52b]

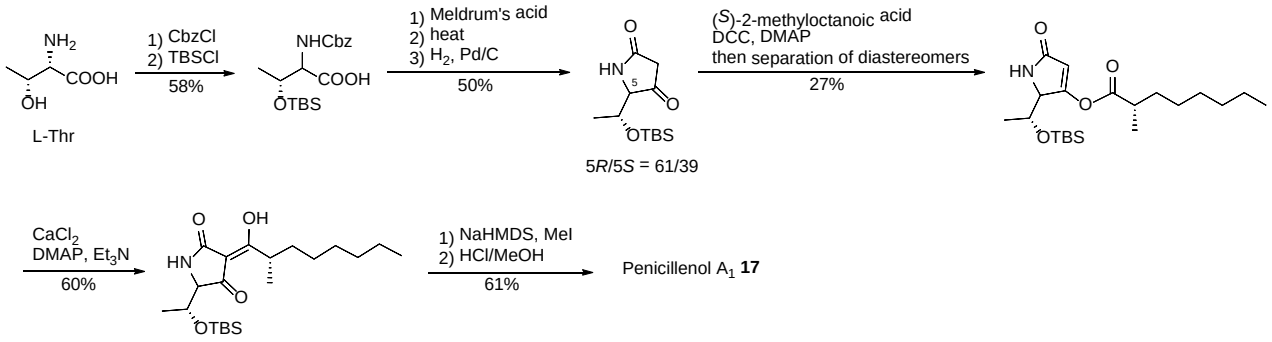


Scheme 11 *Huang's four-step total synthesis of (−)-Chaetominine*: a) 1M NaOH, THF (90%); b) $ClCO_2$, *i*-Bu, NMM (91%); c) $HC(OMe)_3$, $Zn/TiCl_4$, THF (97%); d) DMDO, DMSO, acetone; e) NaOMe, MeOH (90%) or NBS, NaOMe, MeOH (40% unoptimized).

2.1.11 *Penicillenols (17, 18)*

Penicillenols (**17** and **18** Figure 1) were isolated from *Penicillium* sp. GQ-7, an endophytic fungus associated with *Aegiceras corniculatum*.[53] They are pyrrolidine-2,4-dione derivatives (tetramic acid) bearing an α-methyl branched C8-fatty acyl residue at C-3. Penicillenol A_1 **17** and B_1 **18a** have exhibited inhibitory activity against cell lines of HL-60 leukaemia [53]. Both Penicillenol B_1 **18a** and B_2 **18b** have shown equal activity against highly invasive 518A2 melanoma [54] and cisplatin-resistant HT-29 colon carcinoma.[54] Firstly, Yoda and co-workers presented a stereoselective synthesis of Penicillenols A_1 (**17** Scheme 12) in nine steps from *N*,*O*-protected L-threonine with Meldrum's acid and the subsequent 3-acylation of the so-formed tetramic acid.[55] The pivotal step of the synthesis was the improved *O*- to *C*-acyl rearrangement of a 4-*O*-acyltetramic acid derivative using $CaCl_2$ as an effective additive for the formation of the 3-acyltetramic acid bearing a α-methyloctanoyl moiety. Recently, in 2015, Schobert's group reported the first synthesis of **18a** and **18b** in 14 steps by employing an alternative, but longer (10 steps) pathway for the

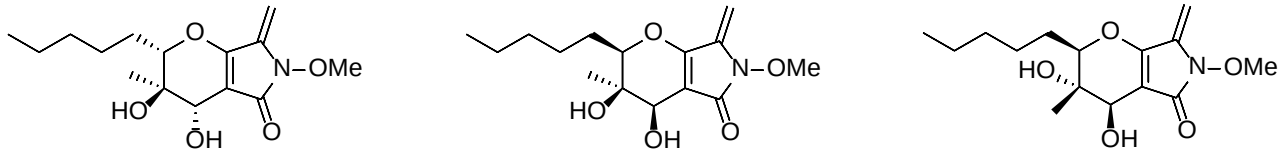
tetramic acid core.[54] The correct configurational assignment of the natural products was carried out by comparing the NMR and optical rotation data of the synthetic products and it was found to be 5*S*,6*R*,9*S* for Penicillenol A_1 **17** [55a] and 9*S* for Penicillenols B **18a** and **18b**.[54]



Scheme 12 *Strategy for the first total stereoselective synthesis of Penicillenol A_1*

2.1.12 *Phaeosphaeride A (19)*

Phaeosphaeride A (**19** Figure 1) was isolated from the endophytic fungus FA39 (*Phaeosphaeria avenaria*) by Clardy's group in 2006.[56] It is an inhibitor of the signal transducer and an activator of transcription 3 (STAT3)-dependent signaling.[57] Since 2011, several research groups have synthesized phaeosphaeride A.[58] All the syntheses developed focused on obtaining phaeosphaeride A with the proposed structure, **53** (Figure 2). However, NMR data for synthetic compounds were not identical to those of the natural product, indicating that the initially proposed structure of natural phaeosphaeride A was incorrect. In 2015, Kogen *et al.* finally established the correct configuration of phaeosphaeride A **19** (Figure 2), altering the originally proposed structure **53** through the total synthesis of *ent*-phaeosphaeride A **54**.[57] During the synthesis, the three adjacent stereocenters were built via Sharpless asymmetric dihydroxylation and the dihydropyran ring was formed via a stereoselective intramolecular vinyl anion aldol reaction.[57]



Phaeosphaeride A ***19*** *correct structure*

Phaeosphaeride A proposed structure up to 2015 ***53***

ent-Phaeosphaeride A ***54***

Figure 2 *Structures of Phaeosphaerides*

2.2 ISOPRENOIDS

Isoprenoids are very widespread in fungi and most of them that feature important antitumor activity derive from endophyte cultures. A large number of these compounds are of great interest because of their biological and chemical properties. Among these, taxol is undoubtetly the most representative of terpenes with antitumor activity. It is well known that many fungal species produce taxol. However, seeing as the main natural source of taxol is a plant, we have decided that a comprehensive discussion on taxol is out of the scope of this review. Therefore, we have chosen to

present the other most intriguing terpens that are characterized by significant anticancer activity and synthesised over the past ten years and have not yet been included in previous reviews, as is in line with the overall target of this overview. The chemical structures of the compounds described are shown in Figure 3.

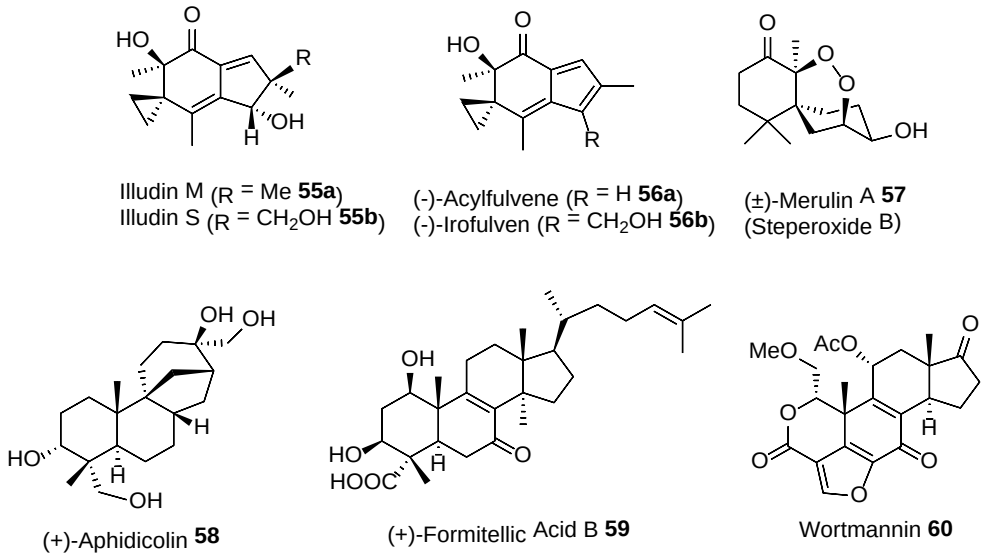


Figure 3 *Structures of the discussed isoprenoids*

2.2.1 *Illudins and Acylfulvenes (55, 56)*

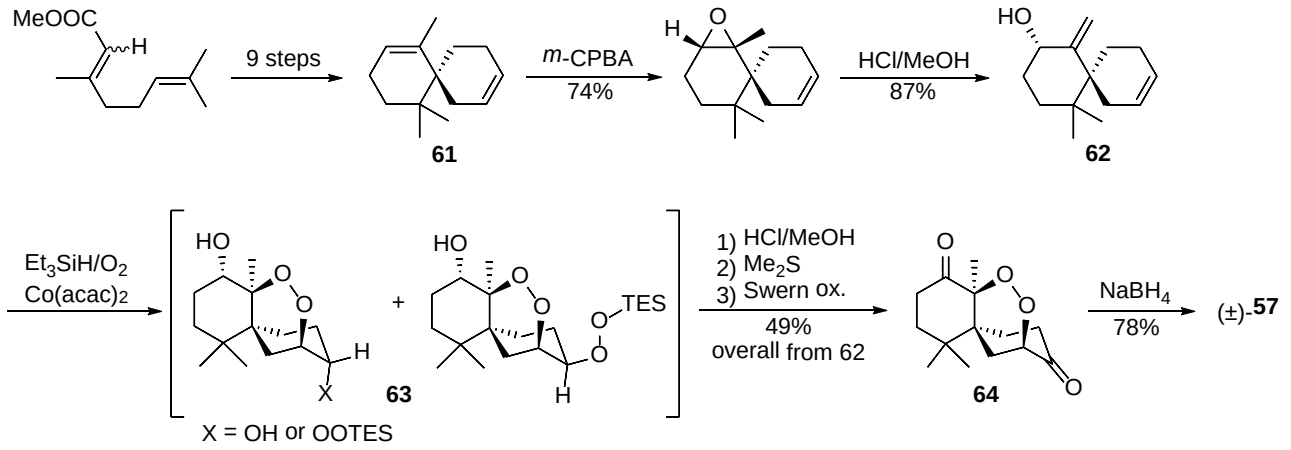
Illudins are a family of highly cytotoxic sesquiterpene secondary metabolites of basidiomycetes. Illudins S and M (**55a** and **55b** Figure 3) are landmarks that belong to this class of compounds and were the first identified from the bioluminescent mushroom *Omphalotus illudens*, in the 1950s [59], and the most cytotoxic members of the family. Acylfulvenes (**56** Figure 3) are semisynthetic derivatives of illudins that were obtained in the course of developing cytotoxic agents with improved therapeutic properties. Recent advances in the synthesis of both illudins and acylfulvenes are thoroughly described in Sturla and Tanasova's review, published in 2012, regarding the chemistry and biology of acylfulvenes.[59] To the best of our knowledge, noteworthy progress has not been reported on the subject since then. We will therefore not discuss the synthetic aspects of these sesquiterpenes any further in this review.

In 2014, Hawkins and co-workers disclosed the use of sterically controlled Diels–Alder cycloadditions of allylidenecyclopropane for provide access to the tricyclic core of illudins.[60]

2.2.2 *Merulin A (57)*

Merulin A (**57** also named steperoxide B, Figure 3) is a sesquiterpenoid belonging to the very recently reported group of chamigrane/norchamigrane endoperoxides.[61] It was isolated from mangrove endophytic fungi *Xylocarpus granatum* [61a] and showed significant cytotoxic activity against human breast cancer and colon cancer cell lines.[61a] In 2015, Wu and Chen reported a synthetic study of several members of the chamigrane family, of which merulin A, which was obtained in racemic form, stands out.[62] Critical steps of the synthetic route are shown in Scheme 13 and feature: *i*) a novel facial selective epoxidation of (±)-norchamigrene **61** that leads to the subsequent and highly-unstable epoxide as a single diastereomer; *ii)* a clean rearrangement of the epoxide to allylol **62**; *iii)* a Co(II)-mediated silylperoxidation which provides the pivotal peroxy bridge-containing ring system **63** of the chamigrane endoperoxide family for the first time; *iv)* a carefully controlled reduction of **64** to yield racemic **57**. The absence of any heteroatoms or additional stereogenic centers in the spirocyclic diene **61** to differentiate the two faces of the reacting C−C double

bond in the epoxidation and the optimal results observed with HCl/MeOH (among cheapest reagents available) in the subsequent rearrangement are quite remarkable. The key intermediate **61** was prepared via a nine-step sequence starting from methyl geranate in a 31% overall yield. In the same work, Wu and Chen carried out the adaptation of the diastereoselective synthesis to an enantioselective one via optically active (*R*)-**61**, which was obtained with a slight modification to Stoltz's method.[62]



Scheme 13 *First synthesis of Merulin A*

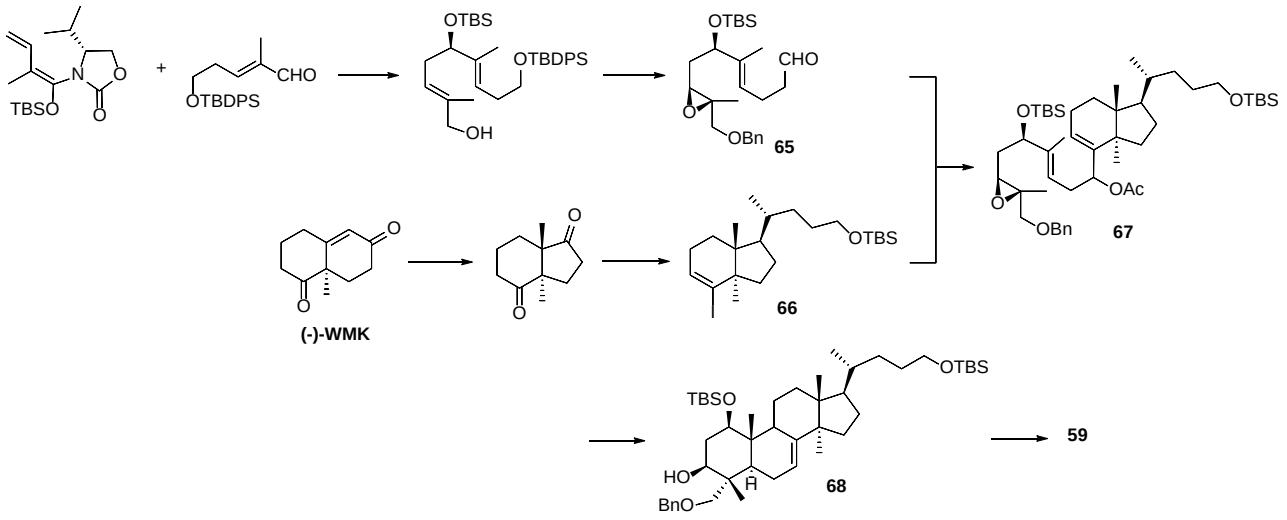
2.2.3 *Aphidicolin (58)*

Aphidicolin (**58** Figure 3) is a tetracyclic diterpenoid metabolite produced by various fungi, including *Cephalosporium aphidicola*, *N. sphaerica* and *Harziella entomophilla*.[3] It reversibly inhibits DNA polymerases *α* and *δ* and therefore has been widely used as a synchronizing agent in experimental systems.[3] Owing to its poor water solubility, it is unsuitable for parenteral administration but its water-soluble analogue, aphidicolin glycinate, has undergone Phase I clinical trials as a synchronizing agent.[3] A complete review of the syntheses of aphidicolin was published by Toyata and Ihara in 1999.[63] A few further advances have been made in the field and have been quoted in a Banerjee *et al.* review which covers the period from 1999 to 2009.[64] In 2009, Little and Zhong described the application of an intramolecular diyl trapping cycloaddition reaction to construct the bicyclo [3.2.1] framework of an aphidicolin synthetic intermediate.[65]

2.2.4 *Formitellic Acid B (59)*

Formitellic acids produced in the mycelium of a basidiomycete *Perenniporia (Fomitella) fraxinea* were originally isolated by Sakaguchi and co-workers.[66] In recent years, they have proven themselves to be potent inhibitors of DNA polymerase and DNA topoisomerases which have been recognized as important enzymatic targets for cancer chemotherapy.[66] Structurally, formitellic acids are triterpenoids which feature a highly oxygenated steroidal AB ring (Figure 3). Concerning the synthetic aspects of this class of compounds, only the asymmetric total synthesis of formitellic acid B (**59** Figure 3) has been accomplished so far and was published by Kobayashi's group in 2009.[67] The central point of the convergent synthesis (Scheme 14) was the coupling of the A/B ring aldehydic precursor **65** with the C/D bicyclic vinyl iodide **66**. The authors coupled these two fragments via the 1,2-addition of the vinyl lithium species, derived from **66**, to the aldehyde **65**. The last two pivotal features were: *i)* the stereoselective synthesis of the tetracyclic intermediate **67** (all requisite chiral centers) via a titanium(III)-mediated radical cascade cyclization of **68**; *ii)* the formation of the enone motif in the B-ring via the isomerization of the olefin, followed by allylic oxidation.

Intermediate **65** was prepared via a stereoselective vinylogous Mukaiyama aldol reaction and a Sharpless asymmetric epoxidation. On the other hand, fragment **66** was stereoselectively synthesized from the dione derived from the (−)-Wieland–Miescher Ketone (WMK). Nevertheless, this synthetic route is very long and consists of a total of almost 30 steps and gives a poor overall yield (4% from **67**).



Scheme 14 *Strategy for the first synthesis of formitellic acid B **59***

2.2.5 *Wortmannin (60)*

Wortmannin (**60** Figure 3) is a furanosteroid initially isolated from *Penicillium wortmannii*, and then afterwards also from *Fusarium torulosum* and *Trichoderma* sp.[3] It is one of the most potent naturally occurring PI3-kinase inhibitors, but is not selective and has shown highly toxicity which has made it difficult to evaluate its *in vivo* activity as an antitumor agent.[3, 68] Wortmannin derivative PX-866 is currently under clinical evaluation.[3] Two excellent reviews regarding the synthetic aspects of wortmannin and itd derivatives were published in 2005[68a] and 2013.[68b] To the best of our knowledge, no new updates have been made, meaning that we consider it redundant to present the syntheses of wortmannin herein.

2.3 QUINONES

Quinone derivative metabolites of fungal endophytes have been reported to inhibit tumor cell lines. We herein review the recent total syntheses of representative examples of these fungal metabolites that have occurred since 2000 to date. They involve benzoquinone (namely torreyanic acid (**69**), tauranin (**70**)), naphthoquinone and anthraquinone derivatives (bikaverin (**71**), rubrofusarin B (**72**), halenaquinone (**73**)), anthraquinones (cytoskyrin A **(74a**), rugulosin (**74b**) and deoxybostrycin (**75**)), macrosporin (**76**), pachybasin (**77**), nidurufin (**78a**), averufin (**78b**), versicolorins (**79**) and topopyrones (**80** and **81**)). The structures of the compounds considered in this section are reported in Figure 4.

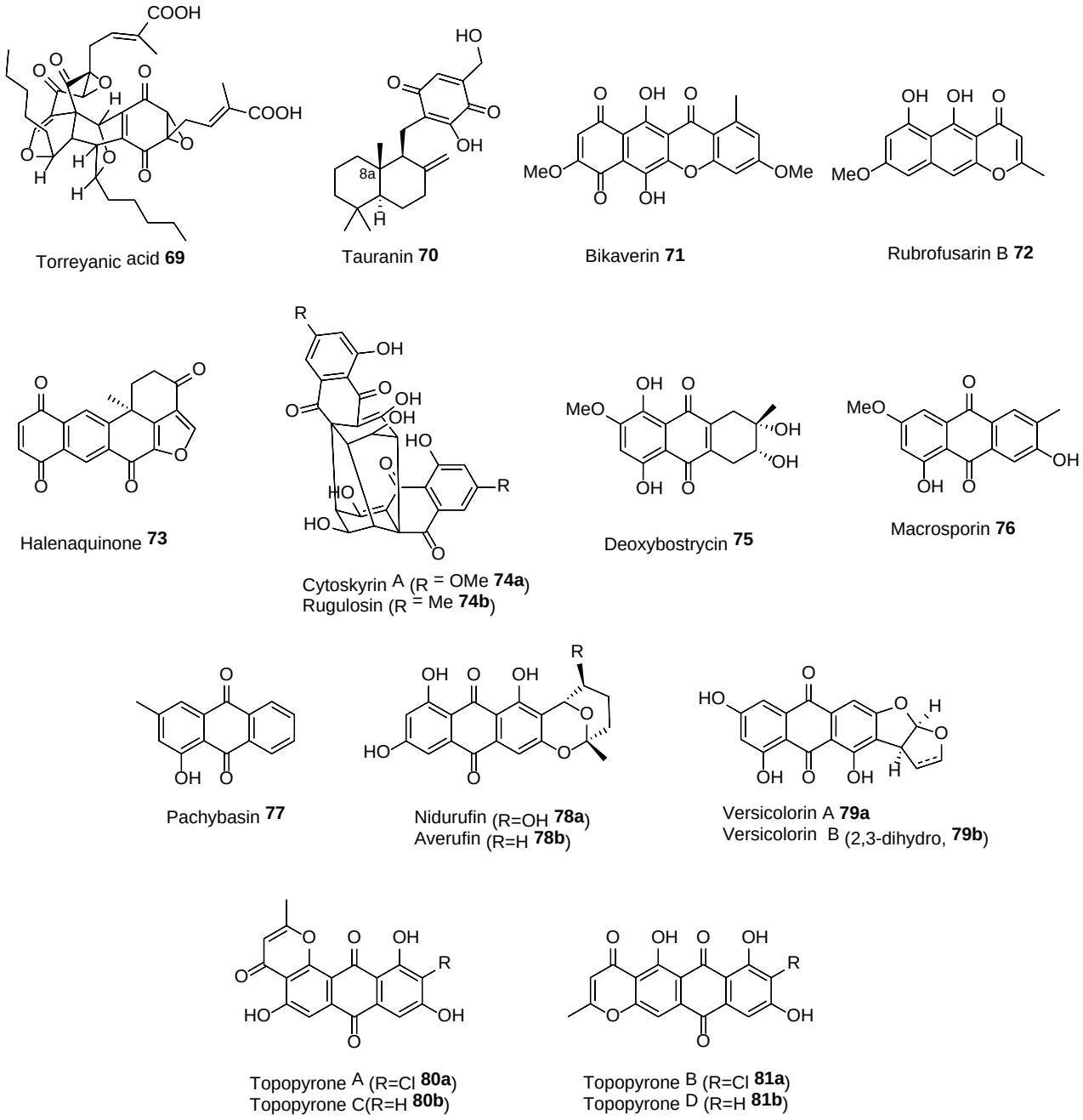


Figure 4 *Structures of the discussed quinones*

2.3.1 *Torreyanic Acid (69)*

Torreyanic acid (**69** Figure 4) is a dimeric epoxybenzoquinone isolated from *Pestalotiopsis* microspore, which is present in *Torreya taxifolia* (a species related to the taxol-producing *Taxus brevifolia*). It showed cytotoxicity against 25 human cancer cell lines and greater activity against cell lines sensitive to protein kinase C (PKC) agonists; it presumably causes cell death by apoptosis.[69]

The first total synthesis of the heptacyclic structure of **69**, which bears 12 oxygen atoms and 8 stereogenic centers, was reported by the group of Porco who obtained both racemic [70] and enantiomeric pure acids.[71] These biomimetic syntheses were based on a sequence of oxidation and electrocyclization steps, followed by a Diels-Alder heterodimerization of key intermediate monomers **82** (Figure 5).

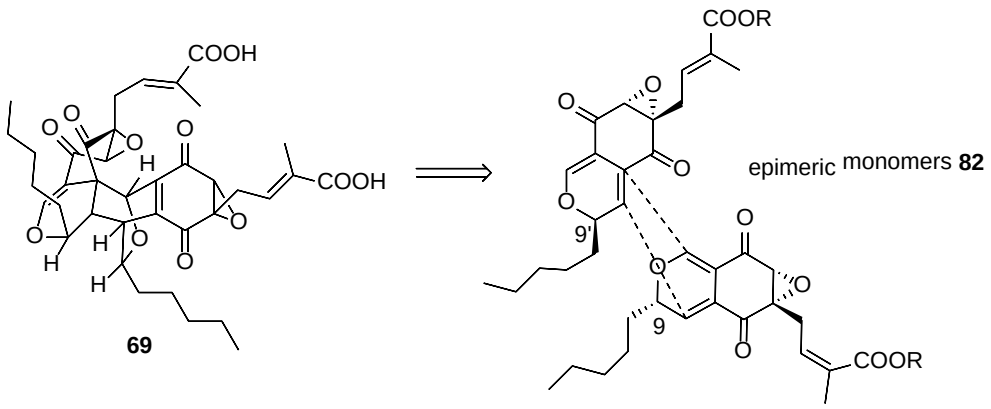
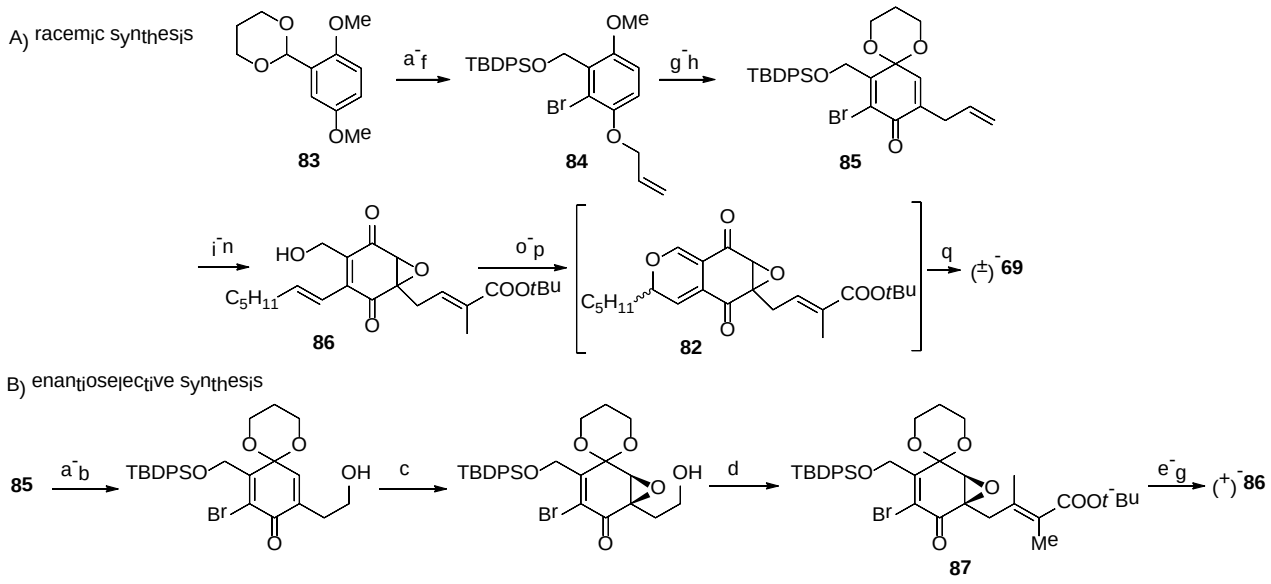


Figure 5

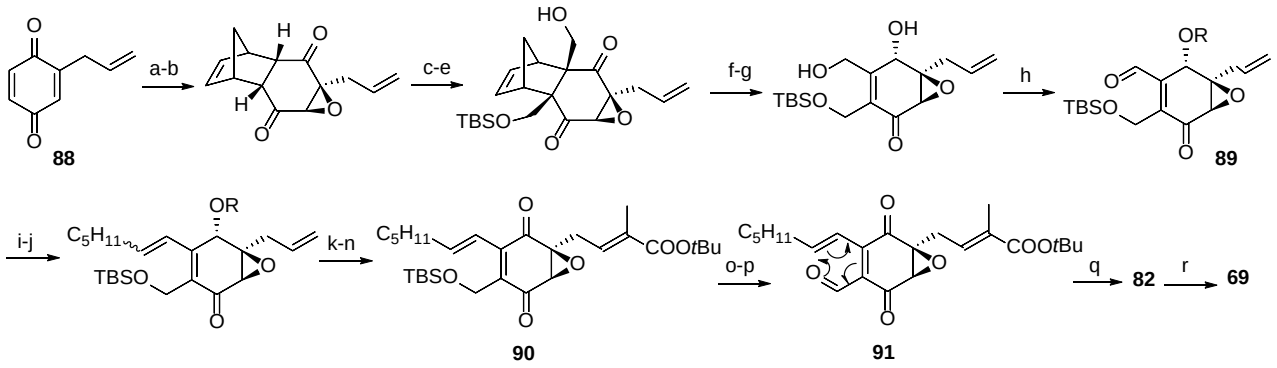
Diastereomeric monomers were prepared, via a multi-step synthesis, from a 1,3-dioxane derivative **83** to the protected hydroquinone precursor **84**. The thermal Claisen rearrangement converted the ortho-allylated phenol directly to the quinone monoacetal **85**. Monoepoxidation and the attachment of the eptenyl side chain afforded the required racemic quinone epoxide **86**.[70] The 2-methyl-2-butenoic acid side chain was then inserted via terminal olefin oxidation, two-carbon homologation and Stille vinylation. After the removal of protecting groups, the required quinone epoxide was oxidised with Dess-Martin periodinane to monomers **82**, which gave two dimeric products. These products, after ester removal, gave racemic torreyanic acid along with its stereoisomer iso-torreyanic acid (Scheme 15, A).



Scheme 15 *Porco's synthesis of torreyanic acid***; A**: a) i. BuLi, 3:1 hexane/benzene, -25 °C, 10 h; ii. $BrCF_2CF_2Br$, THF, 0.5 h, 70%; (b) 13 M HCl, THF, 10 min, 100%; (c) H_2SO_4,70 °C, 14 h, 52%; (d) allyl bromide, K_2CO_3, DMF, 3 h; (e) $NaBH_4$, EtOH, 0.5 h; (f) TBDPSCl, imidazole, DMF, 2.5 h (90% for three steps); (g) (i) neat, 180 °C, 2 h, (ii) $PhI(OAc)_2$, MeOH, 20 min; 70%; (h) $HO(CH_2)_3OH$, PPTS, C_6H_6,80 °C, 20 min, 90%;(i) Ph_3COOH, KHMDS, THF, -78 to -20 °C, 6 h, 81%; (j) catalytic OsO_4, NMO, acetone/H_2O, 25 °C, 15 h; (k) $Pb(OAc)_4$, THF, 15 min, 96%; (l) PPh_3=C(CH_3)COO*t*Bu, DCM, −35 to −10 °C, 4 h, 64%; (m) (*E*)-tributyl-1-heptenyl stannane, $Pd(PPh_3)_4$, $PhCH_3$, 110 °C, 1.5 h, 97%; (n) TBAF/AcOH (1:1), THF, 18 h, 72%; (o) 48% HF, CH_3CN, 15 min, 93%;(p) Dess-Martin periodinane, DCM, 1 h, SiO_2, 80%; (q) TFA/DCM (25:75), 2 h, 100%.
B: (a) $NaIO_4$, OsO_4, THF/H_2O, 1.5 h, 62%; (b) BH_3. *t*$BuNH_2$, MeOH/H_2O, THF, 0 °C, 20 min, 76%; (c) Ph_3COOH, NaHMDS, L-DIPT, 4 Å MS, Tol,–40 °C, 50 h, 91%, 91% ee; (d) (i) Dess-Martin periodinane, DCM, 35 min; (ii) PPh_3=C(CH_3)COO*t*Bu, DCM,–78 to –5°C, 4 h, 94%; (e) (*E*)-tributyl-1-heptenylstannane, $Pd(PPh_3)_4$, Tol, 110 °C, 2 h, 94%; (f) TBAF/AcOH (1:1), THF, 20 h, 76%; (g) 48% aq HF, MeCN, 15 min, 93%.

They were produced by an *endo*-selective [4 + 2] Diels-Alder heterodimerization of monomers **82**, which are epimeric at C9 (C9′). The pentyl chains are *anti* to one another in the [4 + 2] transition state with the dienophile approaching the diene *anti* to the epoxide moiety. The asymmetric total synthesis [71] was achieved from the above reported experimental findings. As expected enantiomeric pure torreyanic acid was synthesized using the non-racemic epoxide (+)-**86**. The enantioselective oxidation was achieved using a tartrate-mediated nucleophilic epoxidation, developed by the same research group. The reaction was carried out on the quinone monoketal **87**, which was obtained from the modification of the allyl side chain (Scheme 15; B).

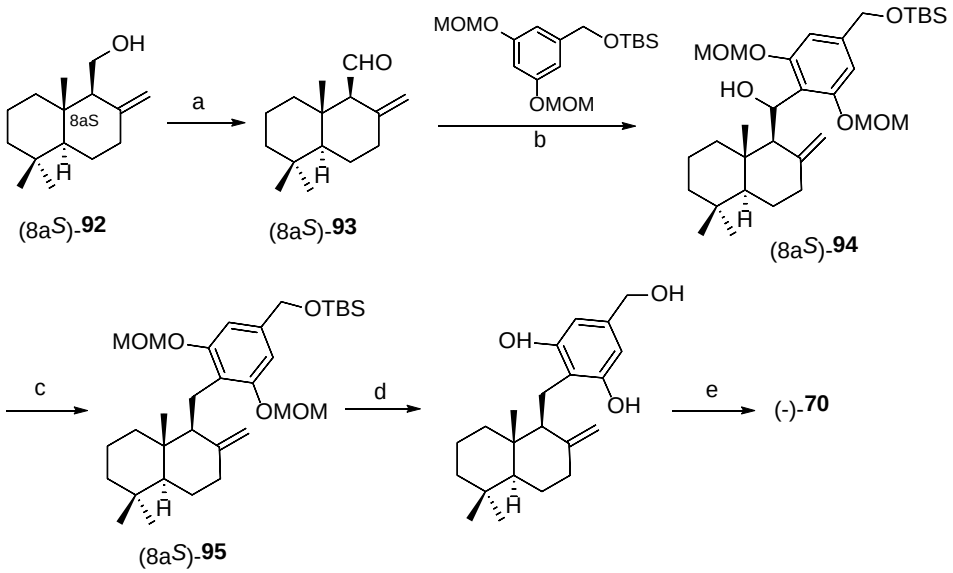
A new total synthesis of (±)-torreyanic acid using a biomimetic approach was reported by Metha [72] in 2004 (Scheme 16). The readily available allyl-substituted *p*-benzoquinone **88**, where the allyl group serves as surrogate of the tiglic residue of the natural product, was converted into a norbornyl scaffold via a Diels-Alder reaction, from which the the stereo-, regio- and chemoselective steps for the synthesis of the epoxyquinone derivative **89** were performed; the *endo*-tricyclic scaffold dictated the *exo*-stereoselectivity. This intermediate was then converted into the required epoxyquinone monomer **90** using a multistep synthesis for the introduction of the tiglic residue and the alkenyl side chain; two steps required photochemical equilibration. Dess-Martin periodinane oxidation finally gave the dienal **91** which give two diastereomeric **82** via a 6π electron cyclization in two disrotatory modes. These rapidly react as in Porco's procedure to give (±)-torreyanic and "iso"torreyanic acid after ester group removal (Scheme 16).



Scheme 16 *Metha's synthesis;* a) Cyclopentadiene, MeOH, 0° C, 98%; b) 10%Na_2CO_3, 30% H_2O_2, acetone, 0 °C, 92%; c) 35% formalin, DBU, THF, 0 °C, 30 min, 95%; d) TBSCl, imidazole, DMAP, DMF, o °C, 90%; e) 35% formalin, DBU, THF, rt, 36 h, 80%; f) $NaBH_4$, MeOH, –5 °C, 84%; g) Et2O, 220 °C, 96%; h) TEMPO, O_2, CuCl, DMF, 90%; i) i. Ac_2O, Py, DMAPP, 98%; ii. *n*-$C_6H_{13}PPh_3Br$, t-BuOK, THF, 0 °C, 65%; j) OsO_4, NMO, –20 °C, 45%; k) hν, 450W (Hanovia), I_2, $CDCl_3$, 80%; l) $Pd(OAc)_4$, THF, 0 °C, 95%; m) $Ph_3P{=}C(Me)CO_2tBu$, –78 to –5°C, 55%; n) i. LiOH, MeOH, –5 °C, 65%; ii. TPAP, NMO, mol sieve 4 Å, 85%,(o) HF, Py, 0 °C, 90%; p) Dess-Martin periodinane, DCM; q) Silica gel, 75% overall; r) TFA, DCM, 100%.

2.3.2 *Tauranin (70)*

The sesquiterpene quinone (-)-tauranin (**70** Figure 4) has been isolated from the mold *Oospora aurantia* and fungus *Phyllosticta spinarum*, an endophytic strain of *Platycladus orientalis*. It has displayed *in vitro* antiproliferative activity against five sentinel cancer cell lines.[73] The total synthesis of (-)-tauranin was reported in 2009 [74], and was enabled by a lipase-catalyzed optical resolution of racemic albicanol (>99% ee), which was developed by the same authors. The Dess–Martin oxidation of (8a*S*)-albicanol (**92**, 99% ee) gave (8a*S*)-albicanal (**93**). Its reaction with an anion, generated from the required aromatic building block, afforded a diastereomeric mixture of (8a*S*)-**94**. The diastereomeric mixture was converted into (8a*S*)-**95**. The deprotection of the methoxymethyl (MOM) group was then investigated and it was found that this step is governed by the concentration of the camphor sulfonic acid used in EtOH. Finally, oxidation by Fremy's salt gave (8a*S*)-**70** (six steps, 31% overall yield) (Scheme 17).

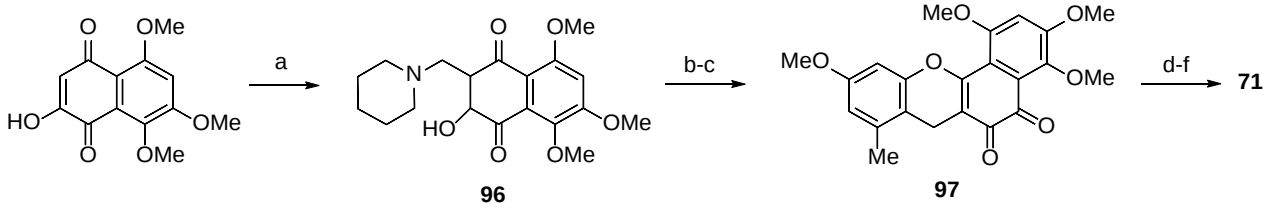


Scheme 17 a) DessMartin periodinane, $NaHCO_3$, 94%; b) n-BuLi, 91%; c) NaHDMS, CS_2, MeI, AlBN, Bu_3SnH, 76%; d) CSA, EtOH, 70%; e) $(KSO_3)_2NO$, phosphate buffer, 63%.

2.3.3 *Bikaverin (71)*

Naphthoquinone bikaverin (**71** Figure 4) is a red pigment that was first obtained from *Gibberella fujikuroi* and then from *Fusarium oxysporum* EPH2RAA in *Ephedra fasciculate* and *Cylindropuntia echinocarpus*.[75] This polyketide showed selective cytoxicity against four sentinel cancer cell lines and has been compared to the standard compound doxorubicin.[75b]

The most recent syntheses of bikaverin were reported in 1992 and 1993. In the first procedure, the non-catalyzed thermal condensation of the Mannich base **96** with 3-methoxy-5-methylphenol and subsequent dehydration gave *o*-quinonic chromene **97**. Isomerization, oxidation and selective dealkylation followed to give bikaverin in a six-step route (Scheme 18).[76]



Scheme 18 a) piperidine, CH_2O; b) 3-methoxy-5-methylphenol, toluene, reflux, 1 h, 40%; c) anhydrous AcOH, 110 °C, 10 min, 100%; d) Toluene, silica, AcOH, 80 °C; e) CrO_3, AcOH, 2 min, 10 °C, 10%; f) LiI, DMF, yield not reported.

The other synthesis was based on a key intermediate phenoxynaphthoquinone, which was subjected to intramolecular acylation, oxidation and dealkylation to regioselectively give bikaverin.[77]

In previous syntheses, the benzo[b]xanthen-12-one scaffold was regiospecifically synthesized via the condensation of (phenylsulfony1)isobenzofuranones with chromones,[78] from the acylation of 1,2,4,5,8-pentamethoxynaphthalene and pyrolysis of the intermediate spyrocompound [79], from orcinol and 3-(2,4,5-trimethoxyphenyl)propiononitrile [80] and from everninic acid and 3,5-dihydroxybenzoic acid.[81]

2.3.4 *Rubrofusarin B (72)*

The naphtha-γ-pyrone rubrofusarin B (**72** Figure 4) (rubrofusarin monomethyl ether) was isolated from *Aspergillus niger* IFB-E003, an endophyte of *Cynodon dactylon*. It was found to be cytotoxic to colon cancer cell line SW1116 and also reversed the multidrug resistance of human epidermal KB carcinoma cells.[82] The first synthesis of rubrofusarin was reported by Shibata in 1963 and 1967, as starting from 2-acetylnaphthalene as the key intermediate [83]. The intermediate was reacted with ethyl acetate and then cyclized to give either rubrofusarin or its mono and dimethyl ethers. A biomimetic synthesis of rubrofusarin B from the orsellinate anion and pyrylium salt was reported in 1984. Although the reaction did not show selectivity, the major product was 2-benzyl-γ-pyrone, which was cyclized to rubrofusarin B using a base that does not open the pyrone ring.[84]

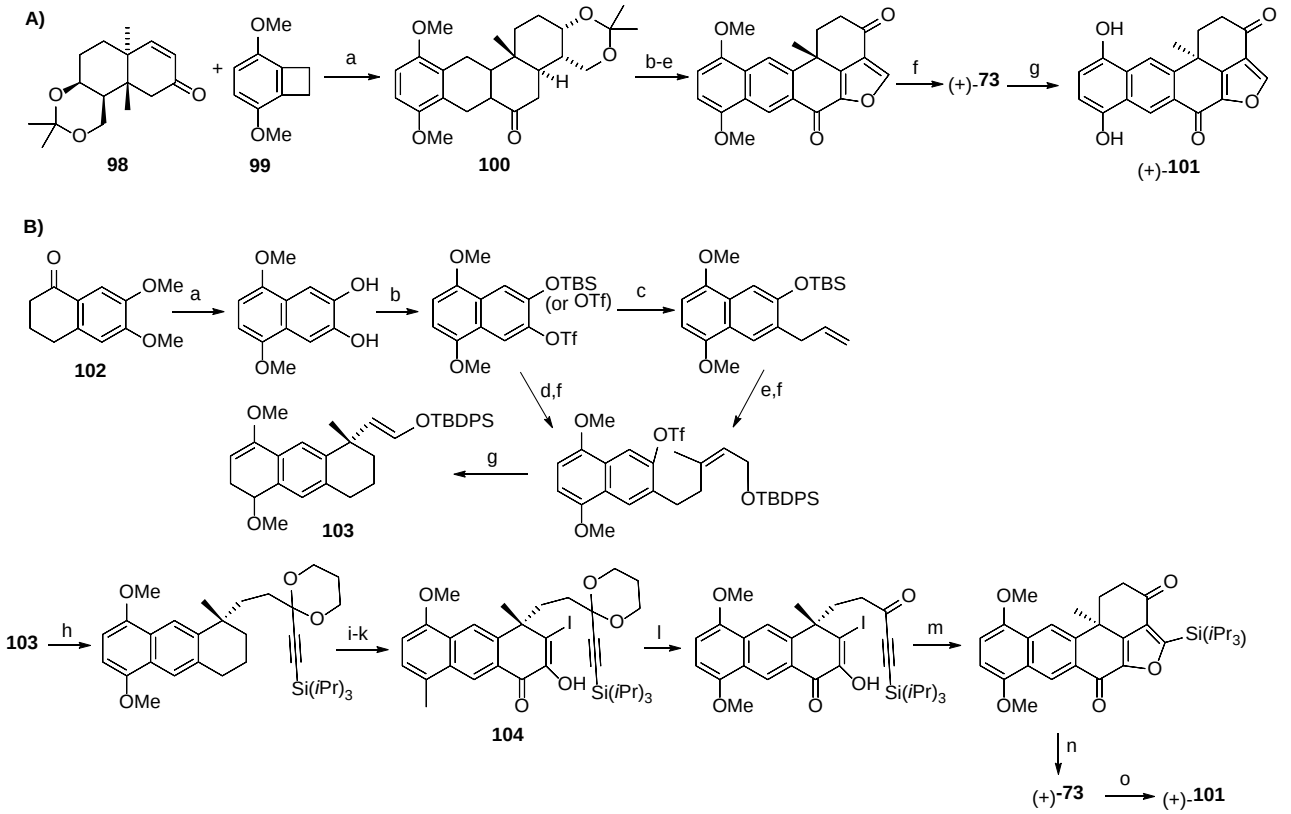
2.3.5 *Halenaquinone (73)*

Halenaquinone (**73** Figure 4) was isolated from two Indo-Pacific collections of the sponge *Xestospongia* cf. *carbonaria* along with other metabolites, all featuring a pentacyclic polyketide skeleton.[85] These natural products were tested for their ability to act as inhibiting agents of various protein tyrosine kinases and halenaquinone was shown not to be a general kinase inhibitor.

The first 15-step total synthesis of (+)-halenaquinone and (+)-halenaquinol (**101**) was reported in 1988, when the tetracyclic structure was obtained from a Diels-Alder reaction between the optically pure dienophile **98** and **99** to afford **100**.[86] (8a*R*)-(-)Wieland-Miescher Ketone was chosen as the starting material for **98** due to the absolute configuration of (+)-**73** and (+)-(**101**) which had previously been theoretically determined. It was converted to enone (+)-(**98**) via a nine-step reaction, including selective protection steps, hydroxymethylation, reduction and oxidation reactions. This was reacted with 3,6-dimethoxybenzocyclobutene (**99**, obtained by a suitable sulfone pyrolysis). The furan ring was formed via the intramolecular cyclization of **100**. The obtained halenaquinol dimethyl ether was finally converted into products **73** and **101** in a sequence of five total steps (Scheme 19, A).

A catalytic asymmetric synthesis of (+)-(**101**) and (+)-(**73**) was reported by Shibasaki in 1998. The starting reagent was the commercially available 6,7-dimethoxy-1-tetralone (**102**).[87] The synthetic procedure was based on a cascade Suzuki cross-coupling/asymmetric Heck reaction/one-pot construction of the required pentacyclic framework from a tricyclic one, **103**, which bears a benzylic quaternary carbon center. Compound **103** was obtained via three different syntheses with 85% ee. Compound **104** then was envisaged as an intermediate for a pentacyclic scaffold synthesis in a one-pot reaction. Therefore, **103** was converted into **104** via a multi-step sequence of reactions (including several steps of group protections). The final cyclization to the desired pentacycle was performed in a single step with a Heck reaction. After desilylation, the product was converted into halenaquinone and halenaquinol (Scheme 19, B).

A short strategy for the synthesis of the furan-fused tetracyclic core of **73** was described and also explored in a model study by Nemoto.[88] The synthesis was based on an intramolecular [4+2] cycloaddition reaction of the *o*-quinodimethane as the key step. A short similar synthesis of (±)-halenaquinone was reported in 2001 and used *o*-benzoquinone monoketals.[89] A concise asymmetric and highly convergent synthesis of (-)-halenaquinone was recently reported as featuring a diastereoselective Heck cyclization and an intramolecular inverse-electron-demand Diels-Alder reaction involving a vinyl quinone.[90]



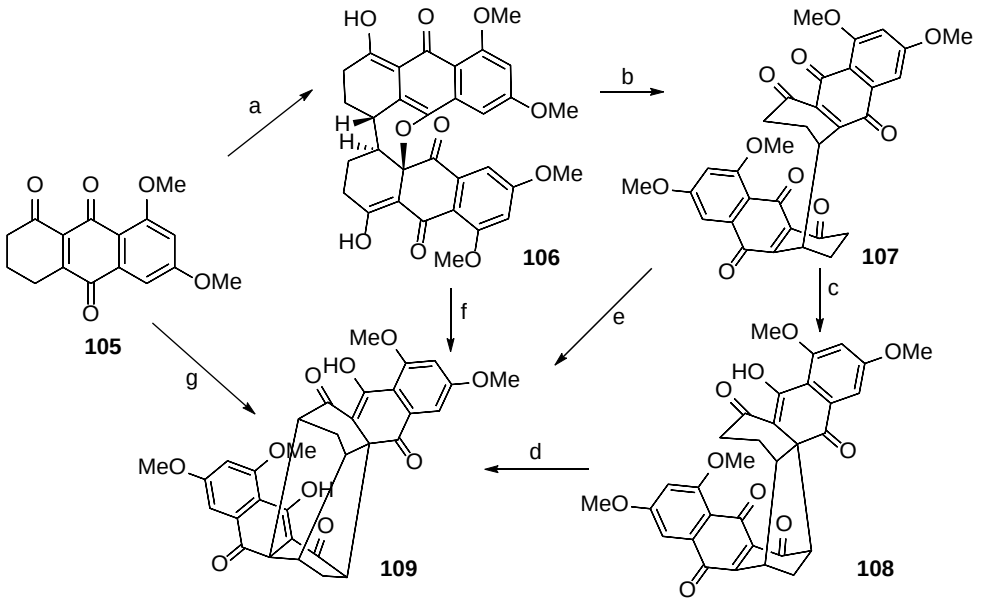
Scheme 19

A: *Shibasaki*'s *synthesis*: a) Benzene, 210-215 °C, 20 h, 33%; b) DDQ, benzene, 89%; c) *t*BuOK, *t*BuOH, 0_2, 90%; d) 60% aqueous AcOH; e) DMSO, DCC, benzene, TFA, Pyr, 44%; f) CAN, aqueous MeOH, 45%; g) aqueous $Na_2S_20_4$, acetone, 100%.

B: *Nemoto's synthesis:* a) five steps, 58% overall yield; b) i. TBSCl, Et_3N, DCM, 0 °C, ii. Tf_2O, Et_3N, DCM, –78 °C to rt, (two steps, 85%); c) CH_2=CHMgBr, $PdCl_2$(dppf).DCM, Et_2O, –78 °C to rt, 100%; d) alkylborane OTBDPS deriv., $PdCl_2$(dppf).DCM, K_2CO_3, THF, 50 °C, 69%; e) 9-BBN, THF, 0 °C to rt, iodoallyl OTBDPS deriv., $PdCl_2$(dppf), DCM, K_3PO_4, THF, 50 °C, 90%; f) i. Bu_4NF, THF, 0°C; ii. Tf_2O, Et_3N, DCM, –78 °C to rt (two steps, 69%); g) $Pd(OAc)_2$, (*S*)-BINAP, K_2CO_3, THF, 60 °C, 22h, 78%; h) five steps, 73% overall yield; i) DDQ, DCM-H_2O, rt, 96%; j) O_2, *t*BuOK, *t*BuOH, 35 °C, 79%; k) NaI, CuSO4, MeOH, H_2O, rt, 97%; l) TsOH.H_2O, acetone, H_2O, 60 °C, 98%; m) $Pd_2(dba)_3$.$CHCl_3$, K_2CO_3, DMF, rt, 72%; n) i. Bu_4NF, AcOH, MeCN, THF, 60 °C, 83%; ii. CAN, MeCN, H_2O, rt, 99%; o) $Na_2S_2O_4$, acetone, H_2O, 0 °C, 100%.

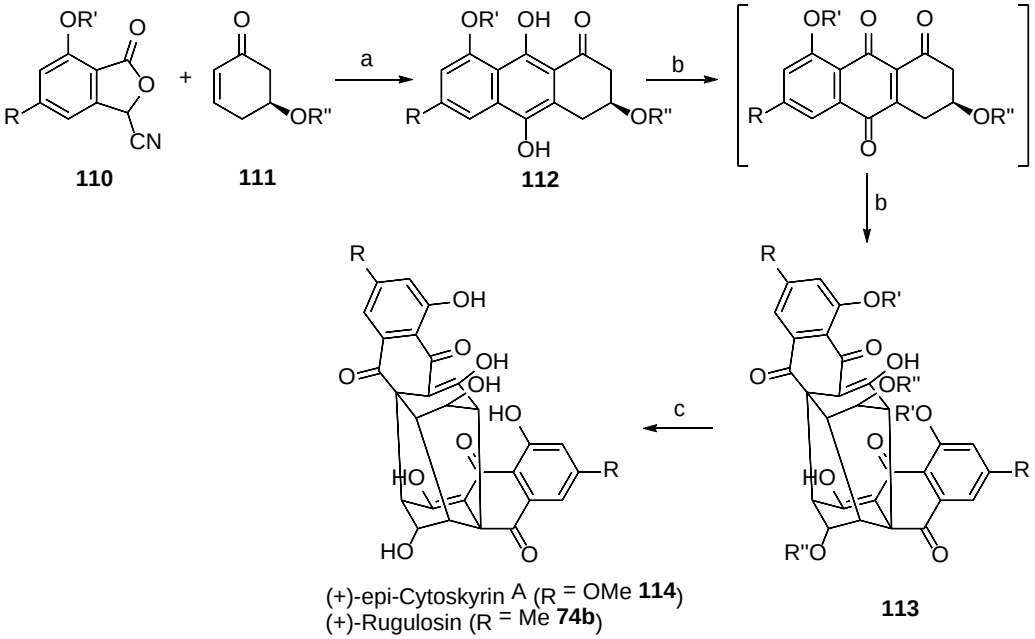
2.3.6 *Cytoskyrin A (74a)* and *Rugulosin (74b)*

Bisanthraquinone cytoskyrin A (**74a** Figure 4) and rugulosin (**74b**) were isolated from *Cytospora* sp. in *Conocarpus erecta* [91] and from *Penicillium islandicum*,[92] respectively. Cytoskyrin exhibited potent DNA-damaging activity and inhibited four human carcinoma cell lines. Their synthesis were developed by Nicolaou in the course of model studies toward cytoskyrin A and 2,2'-epi-cytoskyrin A, although the latter is not a natural product. He discovered that all the bonding patterns found within the above compounds, and other related bisanthraquinones with varying degrees of oxidation and bonding joining, could be selectively formed in controlled one-pot cascade reactions starting from a monomeric anthraquinonic precursor unit.[93] The nonacyclic cytoskyrin model structure was prepared via a five-step cascade sequence involving the transformation of the tricyclic monomer **105** into the nonacyclic system **109** in 66% overall yield. The reaction sequence can be run one-pot or interrupted at each intermediate step.[93c] After initial enolization, stereoselective dimerization to **106** and oxidation to **107** by MnO_2 (excess), an intramolecular double Michael sequence, in the presence of Et_3N (10.0 equiv), afforded the cytoskyrin model scaffold **109** via the intermediate fleeting compounds **107** and **108** (Scheme 20).



Scheme 20 *Nicolaou's synthesis of the nonacyclic cytoskyrin model system **109***: a) CSA, DCM; b) MnO_2; c) Et_3N; d) Et_3N; e) Et_3N; f) MnO_2, Et_3N; g) CSA, MnO_2, Et_3N.

Nicolaou later reported the first biomimetic asymmetric total synthesis of (+)-2,2'-epi-cytoskyrin A using the "cytoskyrin cascade" described above. The model system differed from natural products in its lack of C2 and C2' hydroxyl groups, whose presence could be problematic as aromatization favored their elimination in a total synthesis based on a dimerization of two monomeric units. Various monomeric units were prepared and studied after detailed investigations into the stereochemistry of monomeric anthraquinone dimerization and the nature of the hydroxy protecting groups at C2/C2'. Required fragments **110** and **111**, prepared as reported,[93b] gave dihydroquinone derivatives **112** which, when subjected to the cascade sequence, led to the nonacyclic structure **113** (60% overall yield). (+)-2,2'-epi-cytoskyrin A (**114**) was obtained in a 93% yield after complete deprotection. The same reaction sequence afforded (+)-**74b** (50 % yield over seven steps and 98% after global deprotection) (Scheme 21).[93b, 93d]



Scheme 21 *First biomimetic asymmetric total synthesis of (+)-2,2'-epi-cytoskyrin A*: a) i. LHMDS, THF, 1 h, −78 °C; ii. enone, −78 °C, 1h, to rt; b) i. MnO_2, DCM, 1h, 25 °C; ii. Et_3N, DCM, 25 to 45 °C, 12h; c) HCl conc., MeOH, THF, 60 °C, 12 h.

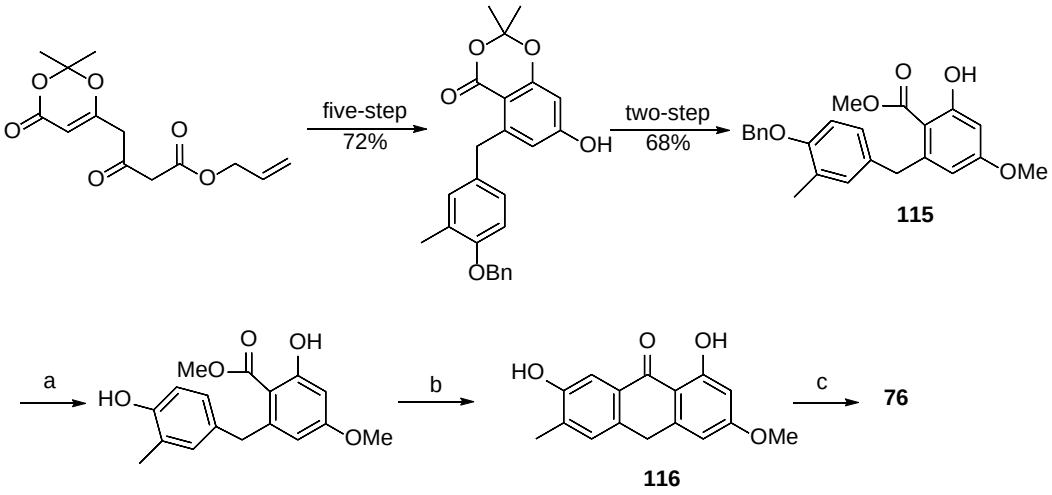
2.3.7 *Deoxybostrycin (75)*

The natural tetrahydroanthraquinone deoxybostrycin (**75** Figure 4) was isolated from the mangrove endophytic fungus *Nigrospora* sp. No. 1403, from the South China Sea, which shows phytotoxic, antimalarial, antimycobacterial and cytotoxic activities.[94] An enantioselective synthesis of (+)-bostrycin was reported as occurring via an asymmetric Diels-Alder reaction, which involved a protected naphthopurpurin and a D-glucose-derived diene.[95] New derivatives were synthesized and their *in vitro* cytotoxicity was tested against three cancer cell lines; most of the compounds exhibited strong cytotoxicity.[96]

2.3.8 *Macrosporin (76)*

The anthracenone macrosporin (**76** Figure 4) was initially isolated from *acrosporium porri* [97] and then from *Alternaria solani*, *Dactylaria lutea*, *Stemphylium eturmiunum*, *Alternaria tomatophilia*, *Ampelomyces* sp., an undetermined fungicolous hyphomycete resembling *Cladosporium* and *Stemphylium globuliferum*. (it is not clear which of the previous fungi this last description refers to) Macrosporin displays moderate cytotoxic activity in L5178Y mouse lymphoma cells.[98]

After the first total synthesis of macrosporin, via the Diels–Alder reaction of a 1,4-naphthoquinone and a diene,[99] a new biomimetic seven-step synthesis has recently been reported as occurring via the initial preparation of 6-benzylresorcylate **115** and its subsequent conversion to anthrone **116** by cyclization and final oxidation to macrosporin (Scheme 22).[100]



Scheme 22 *Total synthesis of macrosporin:* a) H_2, Pd/C, EtOAc, 20 °C, 18 h, 95%; b) TMSOTf, DCM, 20 °C, 18 h, 76%; c) O_2, $CuBr_2$, THF, 20 °C, 20 h, 81%.

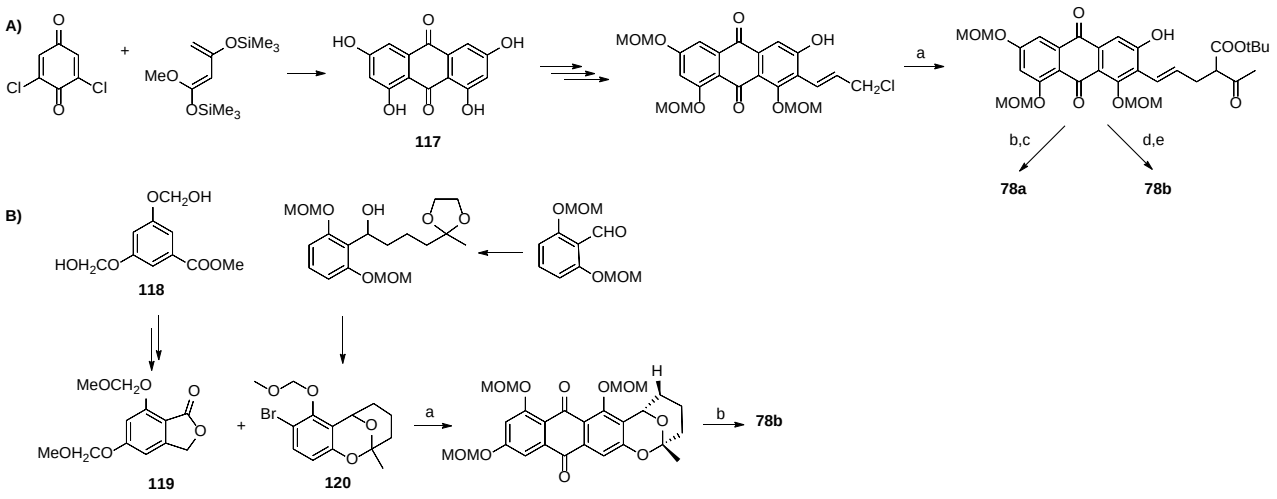
2.3.9 *Pachybasin (77), Nidurufin (78a) and Averufin (78b)*

Many anthracenedione derivatives which show anticancer effects to some extent have been isolated from fungal species. The list includes pachybasin (**77** Figure 4), from mangrove endophytic strains of *Guignardia* sp. and *Halorosellinia* sp. and nidurufin, from a spongiculous strain of *Aspergillus versicolor*, versicolorin A and B, as well as 8-O-methyl- and 6,8-O-dimethylaverufin, produced by a strain of *Penicillium flavidorsum* (syn. *P. glabrum*) recovered

from marine sediments.[1] These compounds are characterized by the presence of a variously oxidized side chain and, in particular, nidurufin and averufin are structurally closely related to 1,3,6,8-tetrahydroxyanthraquinones.

The most recent pachybasin synthesis was reported in 1994, along with that of emodin and other naturally occurring hydroxyl-substituted anthraquinones. These compounds were obtained in high yields via the Diels-Alder reaction of naphthoquinones with substituted butadienyl silyl ketene acetals.[101]

The first synthesis of racemic averufin was accomplished by Brassard via the hydroxyalkylation of 1,3,6,8-tetrahydroxyanthraquinone with 5-oxohexanal at –85°C. Under these conditions, a 6.6% yield of product was isolated.[102] An improved synthesis of 1,3,6,8-tetrahydroxyanthraquinone was reported later. The Diels-Alder reaction in the Brassard synthesis was simplified and the quinone **117** was synthesized on a multigram scale and in a 50% yield.[103] It was then used as a reagent in a new total syntheses of the racemic forms of both averufin and nidurufin (20% and 24% overall yields, respectively (Scheme 23, A). In the modified averufin synthesis, described by Townsend, the key step involved the regiospecific coupling of the phthalide anion of **119** and the benzyne derived *in situ* from aryl bromide **120**. The single isomer anthraquinone precursor of (±)-averufin was obtained thanks to the (methoxymethyl) protecting groups for regiospecific aryl metalation and the subsequent introduction of the electrophile.[104] Averufin was obtained in an 8% overall yield from ester **118** (Scheme 23, B).



Scheme 23 *Averufin and nidurufin syntheses*
A: (a) i. PhSeCl, CCl_4, 0 °C; ii.H_2O, Pyr, tBuAA, NaH, DMSO, rt; (b) AcOH/H_2O (1:1), cat. H_2SO_4; (c) *p*-TosOH Toluene, 90 °C, 50% two-steps yield; (d) *m*-CPBA, DCM, rt; ; (e) AcOH/H_2O (1:1), cat. H_2SO_4.
B: (a) LiTMP, THF, –60 to –40 °C, 35%; (b) aq MeCOOH, H_2SO_4 traces, 85 °C under N_2, 80%.

A formal synthesis of (+)-averufin has recently been reported by Tan and Qiu as occurring in a biosynthetic mimic sequence catalyzed by proline and based on a Knoevenagel condensation and a [4+2] cycloaddition.[105]

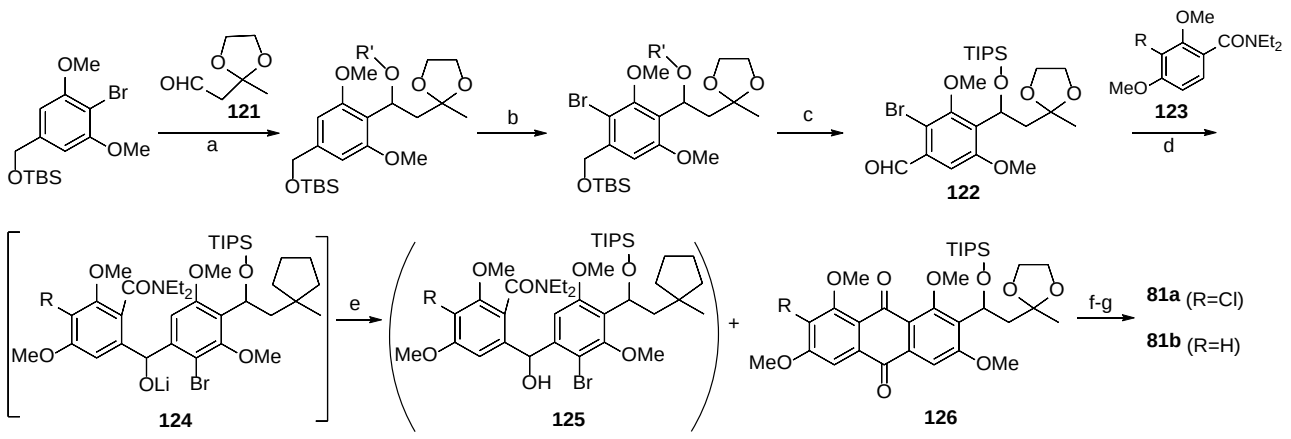
2.3.10 *Versicolorins A (79a) and B (79b)*

Versicolorins A and B (**79** Figure 4) are key precursors in Aflatoxin B_1 and B_2 biosynthesis, which are naturally occurring mycotoxins produced by *Aspergillus flavus*, *A. parasiticus* and *A. nomius*, and are among the most potent carcinogens known. In the course of the elucidation of aflatoxin B_1 biosynthesis [106], Townsend reported the total syntheses of (±)-versicolorin B and (±)-versicolorin A along with other derivatives.[106b] the synthetic strategy involved two silyl triflate-mediated cyclization and rearrangement procedures that allowed both furofuran oxidation states to be produced while avoiding undesired, but thermodynamically favorable, side reactions. In the first procedure,

o-methoxymethylphenylacetaldehyde was cyclized to a five-membered hemiacetal. In the second, this same group, once properly substituted, rearranged to a 4-trialkylsilyloxy-2,5-methano-1,3-benzodioxepane. The sufficient stability of the latter masked the dialdehyde and allowed the construction of the desired aryl ring systems to occur.

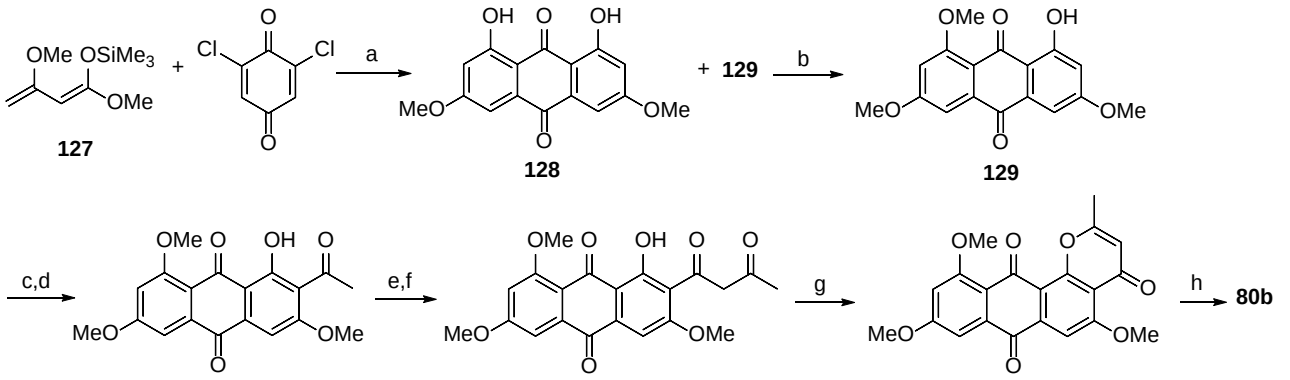
2.3.11 *Topopyrones (80, 81)*

Topopyrones A, B, C and D (**80**, **81** Figure 4) are anthraquinones isolated from cultures of two unidentified strains (*Phoma* sp. and *Penicillium* sp.) [107], whose cytotoxicity is due to the inhibition of topoisomerases. Linearly fused Topopyrones B and D are especially potent and the activity of **81a** against topo-I being is comparable to that of camptothecin. A number of research groups embarked upon their total synthesis. Ciuffolini's research focused on linear compounds.[108] The cyclization of a suitable precursor under equilibrating conditions should only afford linear compounds on the grounds that alkali exposure causes the rearrangement of angular topopyrones A and C to linearly fused B and D (thermodynamically favored) [107]. The anthraquinone core was assembled in a single step via the reaction of **123** with aldehyde **122**, which carried the features common to all topopyrones. Aldehyde **138** was prepared as described in Scheme 24: an organolithium species was added to aldehyde **121**. The straightforward manipulation of the alcohol intermediate gave **122**. The directed metalation of benzamide **123** then gave a Snieckus-type anion, which by reaction with aldehyde **122**, formed the presumed intermediate **124**. Treatment *in situ* with additional *t*-BuLi presumably induced bromine-lithium exchange, thereby triggering cyclization to the corresponding dihydroanthraquinone. Exposure to air finally afforded **126** (17 and 20% yield, R= H and R=Cl), in the one pot three-step syntheses (after purification); corresponding debrominated compounds **125** were however the major products (60-70%). The conversion of **126** to topopyrones D and B was achieved after desilylation, IBX oxidation and final exposure to 48% aqueous HBr solution (Scheme 24).



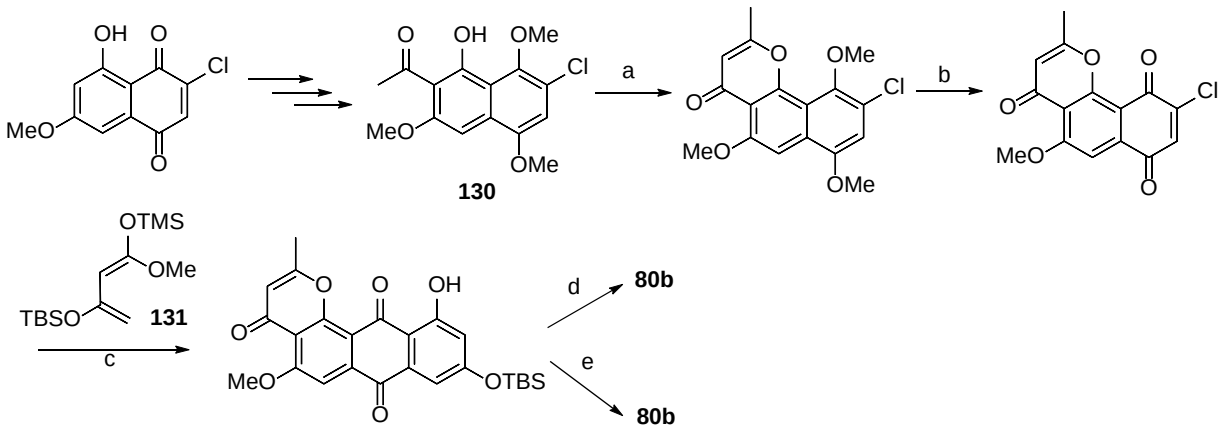
Scheme 24 *Ciuffolini's synthesis of Topopyrones D and B*: a) *t*-BuLi, -78 °C, THF, then **121**, 67%; b) i. TIPS-OTf, imidazole; ii. NBS, MeCN, 94%; c) i. TBAB; ii. Swern oxidation 81%; d) RLi, TMEDA, THF, –78 °C, then **122**; e) *t*-BuLi, –78 °C; f) i. TBAF, THF; ii. IBX, MeCN, reflux; g) 48% aq HBr, AcOH.

The first total synthesis of topopyrone C and analogues was reported by Dallavalle[109]. The synthetic procedure entailed Marschalk alkylation of 1-hydroxy-3,6,8-trimethoxyanthraquinone **129**, Baker–Venkataraman chain elongation and acid-catalyzed cyclization. Quinone **129** was obtained using two successive Diels–Alder cycloadditions between an excess of Brassard diene **127** and 2,6-dichloro-1,4-benzoquinone to obtain a mixture of **129** and **128** after pyrolysis. The mixture was then converted into **129**, using methyl *p*-toluenesulfonate with an overall yield of 40% (Scheme 25).



Scheme 25 *Dallavalle's synthesis of Topopyrone C*: a) i. THF, -78 °C; ii. 130 °C, 10 h; iii. MeOH/HCl 10% 3:1 reflux, 30 min; b) TsOMe, Na_2CO_3, tetraglyme, 140 °C, 2 h, 40%; c) i. NaOH, $Na_2S_2O_4$, MeOH, 0 °C; ii. MeCHO, 20 °C, 3 h; iii. H_2O_2,0 °C, 30%; d) PCC, H_5IO_6, MeCN, 0 °C, 30 min, then rt, 3 h, 60%; e) Ac2O, Py, reflux, 10 h, 88%; f) LiH, THF, reflux, 20 h, 55%; g) CF_3COOH, 0 °C, 20 min, rt, 10 min, 76%; h) BBr_3, DCM, -60 °C, 90 min, 25%.

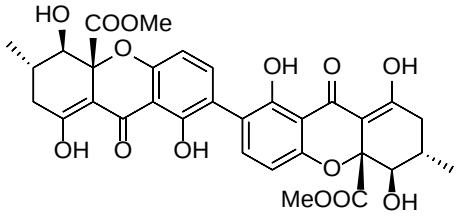
A different strategy was adopted by Hecht for the synthesis of all four natural topopyrones and analogues.[110] The multistep synthesis included a titanium-mediated *ortho*-directed Friedel-Crafts acylation (to give **130**) and Diels-Alder reactions using the novel diene **131**. Topopyrones C and D were synthesized as reported in Scheme 26. Chlorinated topopyrones A and B were synthesized in a similar fashion (**80a** and **81a** Figure 4).



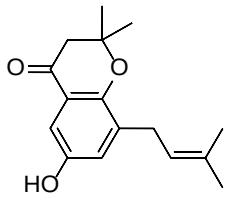
Scheme 26 *Hecht's strategy for Topopyrone synthesis*: a) i. NaH, EtOAc, reflux; ii. TFA, 84% two steps; b) CAN, MeCN, 96%; c) benzene, 70 °C, 54%; d) i. TBAF, THF; ii. BBr_3, DCM, 65% two steps; e) 1% NaOH in MeOH, 70 °C, 3 days, 57%.

2.4 CHROMANOIDS

Flavonoids are a class of polyphenolic compounds that are widely distributed in the plant kingdom as are their endophytes. Of the flavonoids produced by endophytic fungi, xanthones and chromones display antitumor activity. Xanthones are simple tricyclic ring compounds that are structurally related to anthraquinones and characterized by the inclusion of a γ-pyrone nucleus. The dimeric class of ergochromes, whose structure is based on two xanthene monomers linked at positions 2,2', includes ergoflavin and secalonic acids. Isoprenylated chromone derivatives are also interesting and include pestaloficiol J. The structures of flavonoids considered in this review are reported in Figure 6.



Secalonic acid D **132**
Secalonic acid A (the enantiomer)



Pestaloficiol J **133**

Figure 6 *Chemical structures of the discussed chromanoids*

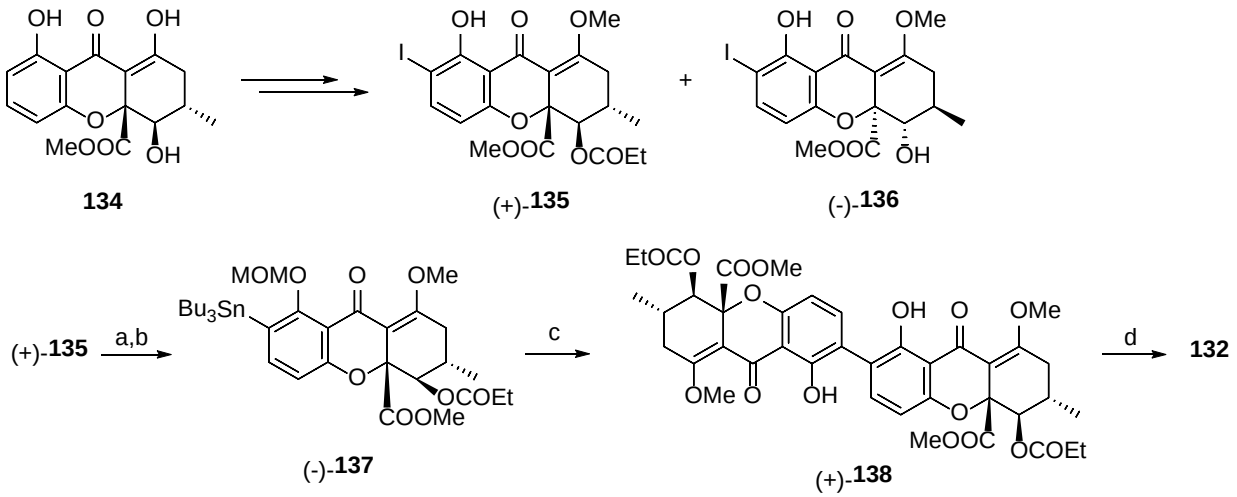
2.4.1 *Secalonic Acid D (132)*

Secalonic acid D (**132** Figure 6) was isolated from *Penicillium oxalicum* in 1970 and was then found in other fungal species [111], and isolated from the mangrove endophytic fungus no. ZSU44. It was found to be extremely toxic and teratogenic, but also potently cytotoxic to human leukemia cells via the induction of apoptosis and the inhibition of DNA topoisomerase I. Its enantiomer, secalonic acid A, has shown significant cytotoxicity to several human cancer cell lines, such as HepG2, A549, Ca Ski, CNE2, MDA-MB-231 (liver cancer, adenocarcinomic, cervical cancer, nasopharyngeal carcinoma and breast cancer cell lines, respectively) [112], while its diastereomer secalonic acid B has antitumor activity.[113] The secalonic acids and other ergochromes have been the subject of hundreds of studies that have focused on both their fascinating structural features and biological activity.

The first total synthesis of secalonic acids D and A, recently reported by Porco, can be regarded as a milestone in the synthesis of dimeric natural products, as the monomeric units are chiral.[113]

The synthetic strategy entailed the preparation of a hemisecalonic derivative (monomeric natural tetrahydroxanthenones such as blennolide A) [114] and then its conversion to the corresponding iodide and stannane.[113, 115] Racemic blennolide **134** (synthesized via the vinylogous addition of siloxyfurans to benzopyryliums and then a Dieckmann cyclization in a maximum of four steps from a 5-hydroxychromone substrate) gave a blennolide derivative via methyl enol ether protection and *ortho*-iodination. Acylative kinetic resolution then provided both (+)-**135** and (-)-**136** in high yields and enantioselectivity (over 99% ee). MOM protection and then stannane formation gave the enantio-enriched tetrahydroxanthone (-)-**137**. Copper-mediated oxidative coupling gave a single dimeric product (+)-**138**. Overall deprotection with HCl provided **132** in a 81% yield (Scheme 27). This procedure achieved a significant synthetic goal, because, as was previously shown, the peculiar electronic nature of the monomeric xanthone framework was not suitable for more direct oxidation reactions. Since the iodide precursor can be pre-activated with trialkyl stannane at the *ortho*-position, the dimerization is thus reliably regioselective. In a similar way, (-)-**136** was converted into secalonic acid A, the enantiomer of secalonic acid D. After MOM protection and stannane synthesis, the intermediate tetrahydroxanthone was obtained (41% yield, two steps). Oxidative coupling led to the dimer (60%yield). Final deprotection with HCl gave secalonic acid A (85% yield).

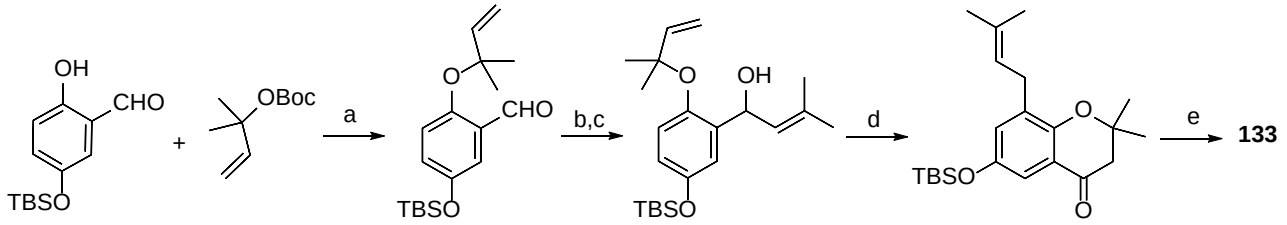
Since secalonic acids C, F, and G, as well as some of the other ergochromes and ergoflavins consist of two nonequivalent monomers, they cannot be prepared via the above synthetic method. The total synthesis of secalonic acid E was reported by Tietze.[116] The 2,4′-and 4,4′-linked variants of the cytotoxic agent secalonic acid A and their analogues have also been synthesized by Porco.[117]



Scheme 27 *Secalonic acid D synthesis*: a) MOMCl, DIEA, DMAP, DCM, rt, 12h, 81%; b) [$Pd_2(dba)_3$], P*t*Bu_3, Bu_4NI, $(SnBu_3)_2$, 1,4-dioxane, 50 °C, 4 h, 56%; c) CuCl, DMA, air, rt, 60%; d) 3M HCl/acetone, 60 °C, 20 h, 81%.

2.4.2 *Pestaloficiol J (133)*

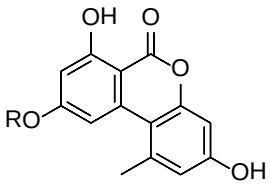
Isoprenylated chromone derivatives (pestaloficiol I, pestaloficiol J, pestaloficiol K and heterodimer pestaloficiol L), were isolated from *Pestalotiopsis fici*, a fungal endophyte of Camellia sinensis. They showed activity against HeLa cells and MCF7 cells, while pestaloficiol J (**133** Figure 6) also displays moderate inhibitory activity against HIV-1 cells. Only **133** has been synthesized. In 2015, it was prepared via a microwave promoted tandem Claisen rearrangement and 6-*endo-dig* cyclization sequence, with an overall six step yield of 38% (Scheme 28).[118]



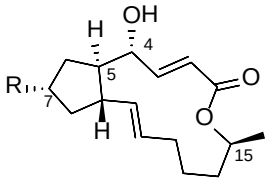
Scheme 28 *Synthesis of Pestaloficiol J*: a) $Pd(PPh_3)_4$, THF, 0 °C, quant.; b) Me_2C=CHMgBr, THF, 0 °C, 80%; c) $(NPr_4)RuO_4$, NMO, 4 Å–MS, 66%; d) $PhNEt_2$, MW (250 °C), 1h, quant; e) TBAF, THF, 0 °C, 93%.

2.5 LACTONIZED KETIDES

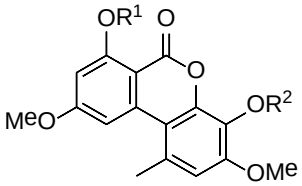
Lactones and esters are widespread fungal metabolites and anticancer activity has been reported in many of them. An overview of the discussed structures is reported in Figure 7.



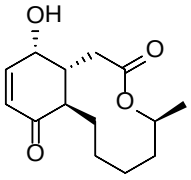
Alternariol (R = H **139a**)
Alternariol 9-methyl ether (R = Me **139b**)



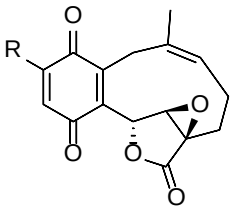
(+)-Brefeldin A (R = OH **140a**)
(+)-Brefeldin C (R = H **140b**)



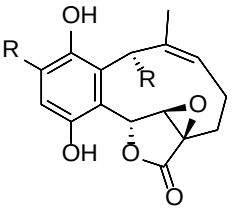
Graphislactone A (R^1=R^2=H **141a**)
Graphislactone B (R^1= Me, R^2=H **141b**)
Graphislactone H (R^1=H, R^2=Me **141c**)



Sch 642305 **142**



Clavilactone B (R =H **143a**)
Clavilactone D (R = OH **143b**)

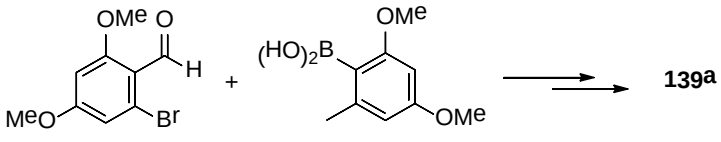


Clavilactone A (R =H **144a**)
Clavilactone C (R = OH **144b**)
Clavilactone E (R = OMe **144c**)

Figure 7 *Chemical structures of the discussed lactonized ketides*

2.5.1 *Alternariol (139)*

The resorcylic lactones alternariol (**139a** Figure 7)[119] and alternariol 9-methyl ether (**139b** Figure 7) are the main metabolites of *Alternaria* fungi. Many syntheses of alternariol have been reported. In 2005, Podlech *et al.* reported the total synthesis of alternariol in seven steps from orcinol and 3,5-dimethoxybromobenzene. The key reaction is a palladium-catalyzed Suzuki-type coupling of an orcinol-derived boronic acid with a brominated resorcylic aldehyde (Scheme 29). The final lactonization and demethylation steps furnished alternariol in a 73% yield.[120]



139a

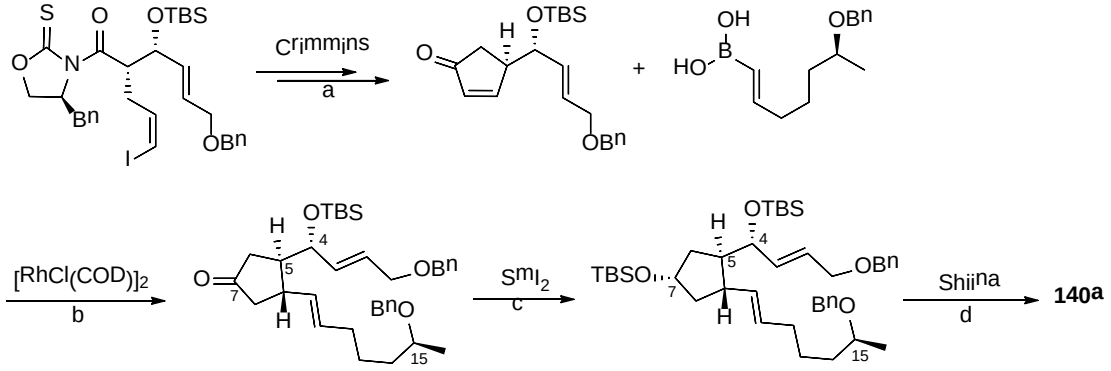
Scheme 29 *Strategy for alternariol synthesis*

A synthetic approach, based on a Pd catatlyzed Suzuki cross coupling, has more recently been proposed in two different papers.[121] Abe and coworkers [121b] reported the synthesis of alternariol via an intramolecular biaryl coupling reaction of the phenyl benzoate derivative and benzoic acid using a palladium reagent. The study of the regioselectivity of the biaryl coupling reaction was also investigated.

2.5.2 *Brefeldins (140)*

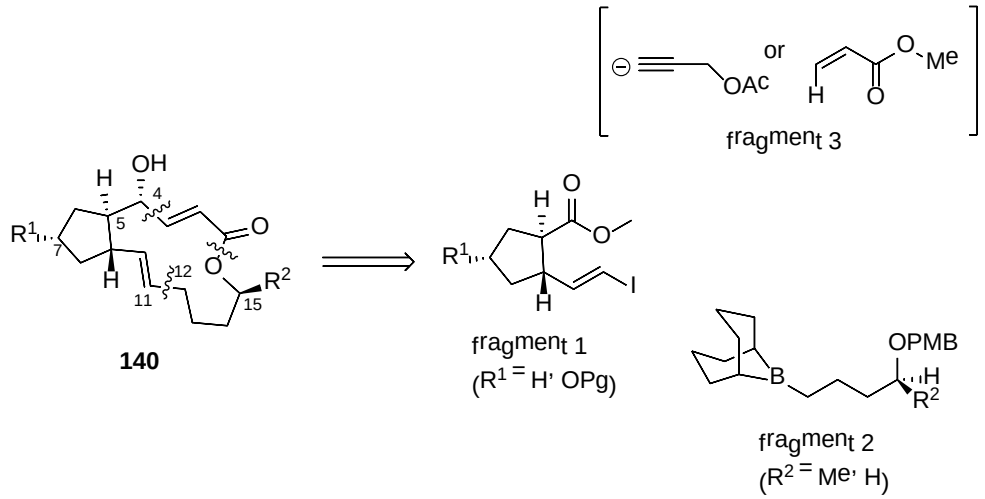
Brefeldin A (BFA, **140a** Figure 7) was first isolated from *Penicillium decumbens* in 1958 [122] and subsequently from many others strains. Although many other names were once given to this compound, brefeldin A has gradually become the only one in use since the 1980s. BFA was shown to possess antifugal, antiviral, antitumor and nematocidal activity since the very earliest reports. Later on in the late 1990s, anticancer activity, including that of suppressing prostatic carcinoma LNCaP cells, was reported. Besides its antitumor effects, BFA has become an important tool for cell biologists as a result of its dramatic effects on the structure and functioning of intracellular organelles, particularly

the Golgi apparatus, and its remarkable ability to inhibit vesicle formation in mammalian cells.[119] Since the first total synthesis of (racemic) BFA by Corey and Wollenberg [123], around 30 total/formal syntheses have been reported in the literature.[124] Interest in probing modes of action and establishing structure-activity relationships has also obviously grown in recent years. Herein, we wish to provide an update of recent developments in the total enantioselective synthesis of brefeldin A. For the syntheses of brefeldin A, its derivatives and analogues published before 2008 see references in Wu *et al.* (2008).[124] These authors reported the total synthesis of **140a** using a multistep approach which features: a) the construction of the five-membered ring from a Crimmins aldol via tandem Li−I exchange and carbanion-mediated cyclization with the concurrent removal of the chiral auxiliary; b) the introduction of the lower side chain (C10 to C16) via the Rh-catalyzed Michael addition of a vinyl boronic acid; c) the stereoselective reduction of the C7 ketone with SmI_2; d) a 2-methyl-6-nitrobenzoic anhydride-mediated lactonization (Scheme 30).



Scheme 30 *Total synthesis of Brefeldin A*: a) *t*-BuLi/Et_2O/-78 °C (75%). b) $RhCl(COD)_2$ 0.03 equiv $MeOH{\cdot}H_2O$, LiOH (95%), c) SmI_2, THF (89%); d) MNBA (2-methyl-6-nitrobenzoic anhydride, DMAP (81%).

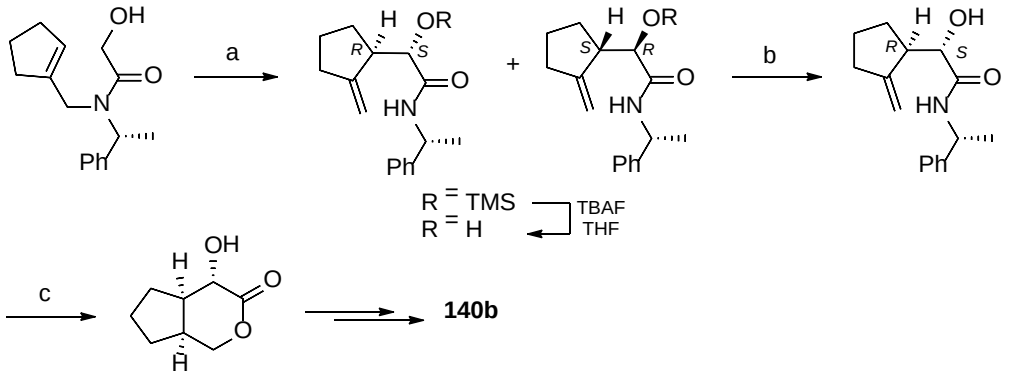
The large majority of the synthetic approaches to brefeldins and its analogues are based on the creation of the C9–C10 or C10–C11 bonds and the C2–C3 or C3–C4 bonds, to create the larger ring of the molecule, which is followed by a final lactonization step. In contrast with these syntheses, Guingant and colleagues proposed an approach featuring the construction of three main fragments, resulting from the sequential disconnection of the C1–O σ bond, as well as the C11–C12 and C3–C4 σ bonds of the macrocyclic lactone , as outlined in Scheme 31.[125]



Scheme 31 *Total synthesis of Brefeldin C: retrosynthetic approach based on sequential disconnection of the C1–O σ bond as well as the C11–C12 and C3–C4 σ bonds.*

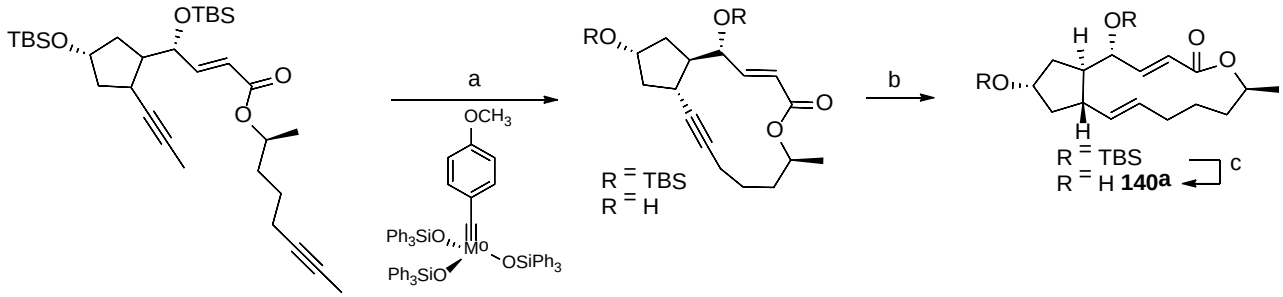
According to this approach, the total synthesis of (+)-brefeldin C was accomplished in 15 steps in a 4.6% overall yield.

In 2011, Tsunoda[126] and coworkers reported the total synthesis of (+)-brefeldin C which used an aza-Claisen rearrangement as the key step. As described in Scheme 32, the precursor was treated with LHMDS (2.5 equiv) at –78 °C and then heated at 65 °C for 36 hours to give the rearranged amide [127] *SR* as the major product along with (*RS*). The diastereomeric mixture of amides was treated with TBAF in THF to give a separable mixture of OH amides, whose ratio was determined, by HPLC analysis, to be 85:15. After separation by SiO_2 column chromatography, the pure amide *SR* was converted to lactone by the hydroboration of the *exo*-olefin with catecholborane, followed by acidic cyclization with *p*-toluenesulfonic acid. Further elaboration led to brefeldin C.



Scheme 32 *Tsunoda's synthesis of brefeldin C*: a) i. LiHMDS (2.5 eq.), toluene, -78 °C. ii. 65 °C, 36 h; b) i. separation, ii. catecholborane, H_2O_2, NaOH, THF (85%); c) TsOH, toluene, 80 °C (89%).

Even more recently, Fuchs and Fuerstner proposed an innovative approach to the establishment of the *E* stereochemistry of the macrolactone of brefeldin A and C.[128] Ring-Closing olefin Metathesis (RCM) at the C10-11 bond is the only catalytic method used to synthesize the macrocycle to date.[129] Unfortunately, the reaction is poorly stereoselective and, as a consequence, the observed isomer ratios were case dependent and typically unfavorable. The procedure for direct alkyne *trans*-hydrogenation proposed by Fuestner *et al.* (Scheme 33) consists of a ruthenium-catalyzed *trans*-hydrogenation that is selective for the triple bond (the transannular alkene and the lactone site of the cycloalkyne precursors are not compromised). (please check meaning)



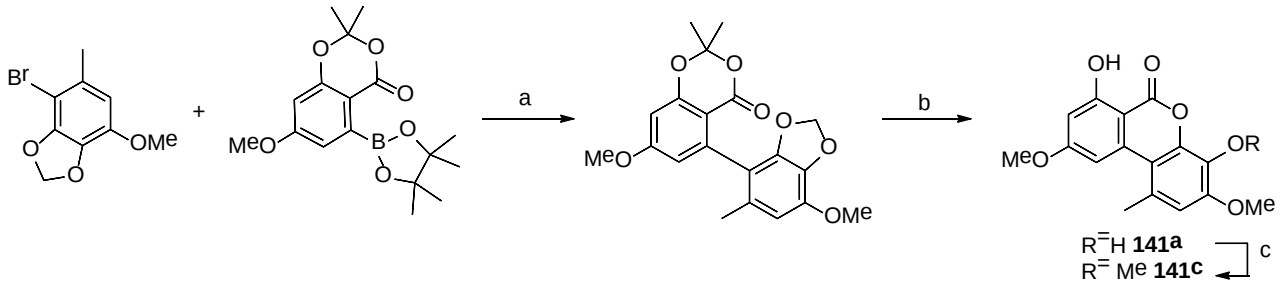
Scheme 33 *Fuestner's synthesis of brefeldin A*: a) molybdenum alkylidyne complex catalyst (5 mol %), toluene, MS 5 , 80 °C (67 %, 1.25 g scale); b) H_2 (30 atm), $[CpRu(MeCN)_3]PF_6$, DCM (56%, 1.15 g scale); c) HCl aq, THF (94%).

Cycloalkynes were used as the substrate for the crucial *trans*-hydrogenation. [CpRu(cod)Cl] was identified as a good catalyst for this transformation and furnished the product with excellent selectivity (E:Z>99:1). The equally reducible enoate moiety was not touched to any noticeable extent nor was the lactone cleaved by the Lewis-acidic catalyst species

that was generated *in situ*. Standard deprotection then furnished **163a** as a colorless crystalline material, as confirmed by X-ray diffraction.

2.5.3 *Graphislactones (141)*

Graphislactones are a family of natural compounds whose basic framework consists of 6H-dibenzo[b,d]pyran-6-one. Graphislactone A (**141a** Figure 7) was first isolated as a natural product from the lichen *Graphis scripta var. pulverulenta* in the late 1990s. Graphislacton H (**141c** Figure 7) has been isolated from the endophytic fungus *Cephalos- porium acemonium* IFB-E007. The biosynthesis of graphislactones is strongly related to that of Alternaria metabolites. In fact, as depicted in Figure 7, their structures are very similar and 3-desmethylgraphislactone A has been identified in the metabolism of Alternaria toxins. A number of different types of biological activity have been reported for graphislactones and related compounds. Graphislactone A is an antioxidant and a scavenger of free radicals, while graphislactones A, G and H have been found to be active against the SW1116 cell line, and graphislactone A and botrallin are moderate inhibitors of AChE.[130] In 2009, Podlech *et al.* [130b] proposed the synthesis of some members of the family of graphislactones, including graphislactone A and H (Scheme 34). The synthetic approach is based on a Suzuki coupling between two previously synthesized fragments.

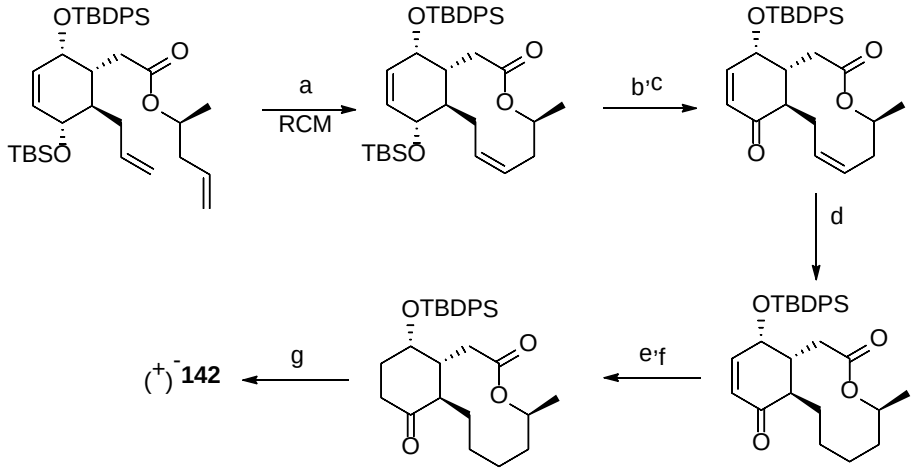


Scheme 34 *Syntheses of Graphislactone A and H*: a) $Pd(Ph_3)_4$, Cs_2CO_3 (83%); b) BCl_3 (39%); c) CH_2N_2 (quant).

The total synthesis of graphislactone A was thus be completed in 10 steps and in a 16% yield. The synthesis of graphislactone H was achieved for the first time via the methylation of graphislactone A with diazomethane in a quantitative yield. The total synthesis was completed in 11 steps and a 16% yield. A similar approach was used by the same group to synthesize graphislactone G, a chlorinated resorcylic lactone.[131]

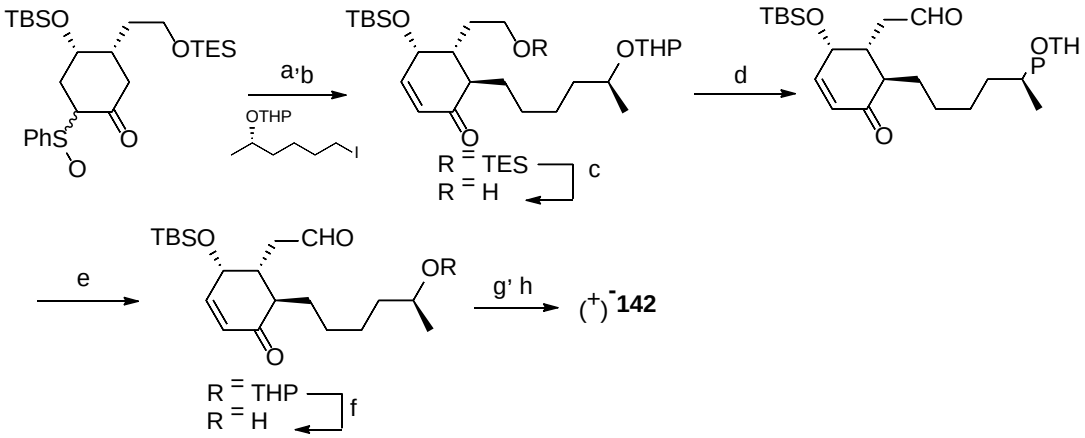
2.5.4 *Sch 642305 (142)*

Towards the end of 2003, the isolation and structure elucidation of a novel natural product, Sch 642305 (**142** Figure 7), which was isolated from the fermentation broth of the fungus *Penicillium verrucosum* (culture ILF-16214), has been reported.[132] Compound **142** exhibited inhibitory activity against the *Escherichia coli* bacterial DNA primase enzyme. It should also be pointed out that very few natural products exhibiting DnaG inhibition activity have been reported so far. Furthermore, a more recent report indicates that Sch 642305, isolated this time from the fungus *Septofusidium* sp., exhibits inhibition of HIV-1 Tat-dependent transactivation.[133] HIV-1 Tat is essential for viral replication, making the Tat-protein is a challenging target for the development of new therapeutics for the treatment of HIV infection.[133] From a purely structural perspective, Sch 642305 consists of a decalactone moiety fused to a 4-hydroxycyclo-hexenone ring. The additional presence of four stereogenic centers makes it a challenging and attractive synthetic goal. One of the most recent syntheses found in the literature, the report by Metha *et al.* [134] of the enantioselective total synthesis of Sch 642305 is based on a RCM protocol to construct the key decalactone moiety (Scheme 35).



Scheme 35 *Metha's synthesis of Sch 642305*: a) Grubbs II catalyst (10 mol%), DCM, reflux, 2 h, 84%; b) $PdCl_2(CH_3CN)_2$, moist acetone, rt, 5 h, 94%; c) Dess–Martin periodinane, DCM, 0 °C, 6 h, 95%; d) 10% Pd/C, H_2, EtOAc, 96%; e) LHMDS, PhSeCl, THF, 278 °C; f) H_2O_2, pyridine, DCM, 0 °C, 10 min (78% two steps); g) TBAF–AcOH (1 : 1), THF, RT, 8 h, 91%.

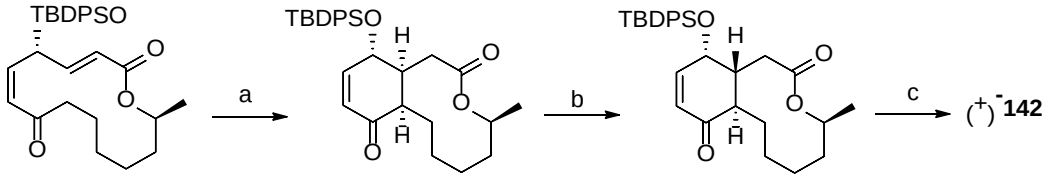
The substrate was exposed to the second generation Grubbs catalyst and which enabled the bicyclic framework to be formed, embedding the decalactone moiety. Further synthetic elaboration, as described in Scheme 41, furnished the target molecule (+)-**142**. The synthetic compound was found to be spectroscopically identical to the natural product. A complementary synthesis, in which the formation of the macrolide is based on a lactonization process, has been proposed by Watanabe *et al.* (Scheme 36).[135] The stereoselective synthesis of Sch 642305 started from a chiral alkyl iodide obtained by chiral reduction using baker's yeast and used to alkylate a β-ketosulfoxide via a dianion procedure. The product was obtained with the desired stereochemistry and was used as a substrate for the following Yamaguchi lactonization. The overall yield was 10% after 18 steps which started from the chiral building block.



Scheme 36 *Watanable's stereoselective synthesis of Sch 642305*: a) LDA, THF; b) $CaCO_3$, toluene (47% in two steps); c) HF, CH_3CN (98%); d) Dess–Martin periodinane, CH_2Cl_2 (84%); e) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, *tert*-BuOH, water (90%); f) $MgBr_2 \cdot Et_2O$, ether (quant); g) 2,4,6-trichlorobenzoylchloride, NEt_3, THF then DMAP, toluene (73%); h) TBAF, AcOH, THF (87%).

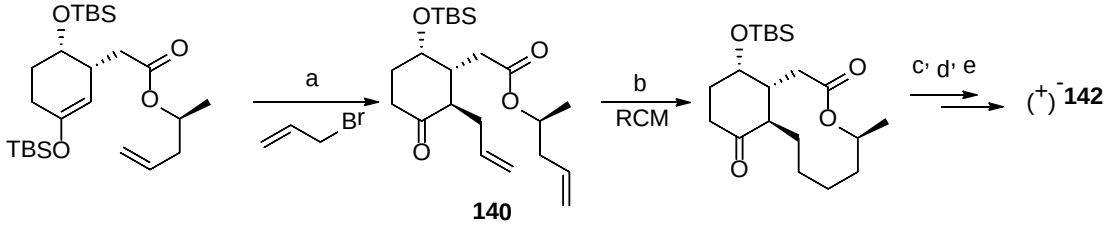
It is worth mentioning that the synthesis of (+)-Sch 642305 was completed in 17 steps in a 1.6% overall yield by Snider *et al.* in 2006.[136] The transannular Michael reaction of the macrolactone represented in Scheme 37 with NaH in THF

provided cyclohexenone stereospecifically. The treatment of cyclohexanone, which was obtained in TFA/$CDCl_3$, provided a 3:1 equilibrium mixture of diastereoisomers. Upon separation, the diastereoisomer of interest was hydrolyzed to give (+)-Sch 642305.



Scheme 37 *Snider's synthesis of Sch 642305*: a) 1.2 eq. NaH, THF, 0 °C, 30 min; b) 1.5% TFA, $CDCl_3$, 120 °C, 3h; c) TBAF, HOAc, THF.

The most recent papers on the synthesis of Sch 642305 appeared in 2007. Kita *et al.* proposed the enantioselective synthesis of (+)-Sch 642305. The chiral non-racemic hydrobenzoin was used as a chiral auxiliary for multiple purposes: a) the desymmetrization of the diene, b) a template for attaining regio- and stereoselective reactions, c) as an oxygen source at the C4-position, and d) as a protecting group for the hydroxyl functions. In particular, the chiral auxiliary played a role in every step throughout the synthesis.[137] In the same year, Trauner *et al.* proposed a highly convergent, enantioselective synthesis of (+)-Sch 642305 which featured a Mukaiyama−Michael addition followed by allylation to establish the *syn*−*anti* relationship of the three contiguous stereocenters.[138] As shown previously, the 10-membered macrolactone was instead formed via ring-closing metathesis (Scheme 38).[134]



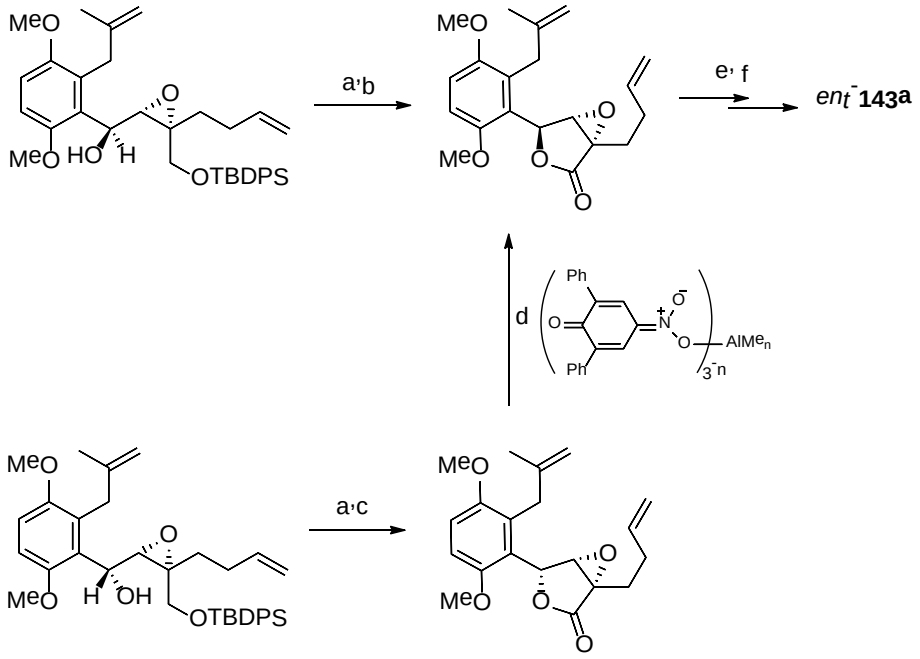
Scheme 38 *Trauner's enantioselective synthesis of Sch 642305*: a) TASF (56%); b) Grubbs II (63%); c) H_2, Pd-C (96%); d) NaHMDS, TESCl, $Pd(OAc)_2$ (61%); e) TBAF-AcOH (73%).

Starting silyl enol ether was subjected to stereoselective allylation with allyl bromide in the presence of TASF, giving cyclohexanone **145** in good yield and with excellent diastereoselectivity. This was then used as a substrate for a RCM reaction with a second generation Grubbs catalyst, which led to the desired isomer, although all previous steps were performed on inseparable mixtures of *syn*- and *anti*- isomers, with respect to the C4-C5 stereo- centers. The corresponding *anti*-isomer was presumably lost in the RCM step. The resulting *cis*-alkene underwent hydrogenation, dehydrogenation and deprotection to complete the synthesis.

2.5.5 *Clavilactones (143, 144)*

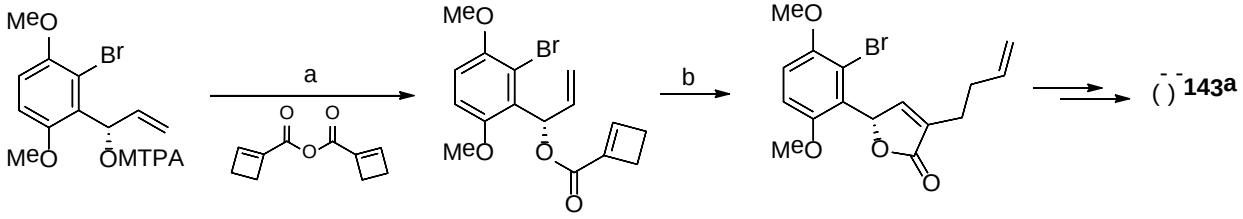
A series of cyclic bioactive compounds, clavilactones A, B and C (**144a**, **143a** and **144b** respectively, Figure 7), were first isolated in 1994 as antifungal and antibacterial constituents in a culture of the non-toxigenic fungus *Clitocybe clavipes*.[139] The isolation of structurally related clavilactones D and E (**143b** and **144c** respectively, Figure 7) from the same fungus, but grown in a different culture medium, has recently been accomplished.[140] Clavilactones A, B and D have shown potent inhibitory activity toward the epidermal growth factor receptor [104] tyrosine kinase, which is

responsible for cellular transduction pathways, thereby underscoring their relevance to medicinal applications.[141] Clavilactone structures contain a constrained ten-membered ring fused to a 2,3-epoxy-γ-lactone and a benzoquinone or hydroquinone. In 2006, Barrett *et al.* [142] reported the total synthesis of *ent*-clavilactone B ((+)-*ent*-**138a** Figure 7) and the assignment of absolute stereochemistry.



Scheme 39 *Barrett's synthesis of ent-clavilactone B*: a) Bu_4NF (TBAF), THF; b) TEMPO (20 mol %), $PhI(OAc)_2$, DCM (69% two steps); c) Pr_4NRuO_4 (TPAP) (15 mol %), NMO, 4 Å MS, MeCN, 74%; d) DCM (80%); (e) $Cl_2(Cy_3P)$(sIMes)RudCHPh (40 mol %), tetrafluorobenzoquinone (80 mol %), PhMe, 80 °C (65%); f) CAN, MeCN, H_2O (74%).

The tri-substituted alkene C11-C12 of clavilactone B was made available by means of a ring closing metathesis reaction (RCM) from a diene precursor in the presence of Grubbs' second generation catalyst, in a 65% yield (Scheme 39). The NMR spectra of the compound obtained were compared with those of a sample derived from the natural product and complete correlation was found. Consequently, the absolute configuration of the natural product was unambiguously assigned as 6*R*, 7*R*, 8*R*. The first total synthesis of the natural enantiomers of clavilactones A and B ((+)-**144a** and (-)-**143a** respectively Figure 7) was recently accomplished using a conceptually novel method that relies on ring-opening/ring-closing metathesis (ROM/RCM) (Scheme 40).[143]

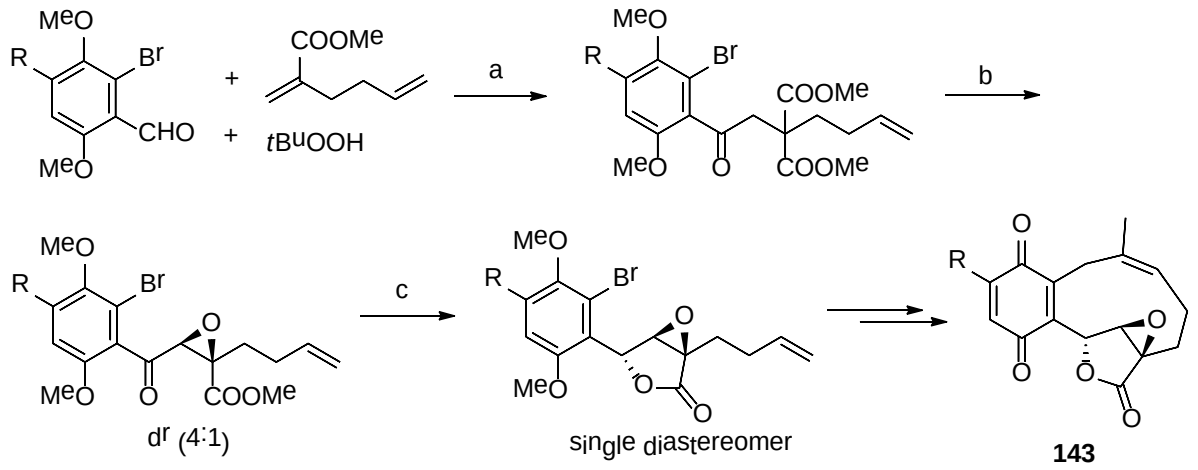


Scheme 40 *Synthesis of (-)-clavilactone B via ROM/RCM*: a) LDA, cyclobuten anhydride, -78 °C to 0 °C (85%); b) i. 1st Grubb's cat (10 mol %), toluene (0.01 M), 80 °C, 5h. ii. Ethylene (1 atm), 2nd Grubbs Catalysts, 80 °C (76%).

The one-pot ROM/RCM in toluene using the first-generation Grubbs catalyst, followed by the treatment of the resulting mixture with ethylene (1 atm) and the second-generation Grubbs catalyst (5 mol %), produced the desired product in

good yield (76%). The approach has been also used to synthesize clavilactone A (in 15 steps with 1.6% yield).

Clavilactones A, B, and D have also been synthesized via the iron-catalyzed carbonylation-peroxidation of a 1,5-diene in three steps .[144]. The synthesis began with a three-component reaction, as shown in Scheme 41, which used $FeCl_2$ as the catalyst. A pyrrolidine-catalyzed epoxidation, followed by a $NaBH_4$-mediated reductive lactonization, furnished α,β−epoxy-γ-butyrolactones. The chelation between the carbonyl and the epoxy group and the boron atom allows the hydride to attack the less hindered side of the carbonyl. The total synthesis of (±) clavilactone B was completed in 6 steps and a 15.1 % yield, while 7 steps were needed to give (±) clavilactone A in a 14.9 % yield,and 7 steps again and a 15.5 % yield for (±) the proposed clavilactone D. The total synthesis of clavilactone D allowed the 3-position of the quinone ring to be established as the correct position of the OH group instead of the 2-position.



Scheme 41 a) $FeCl_2$, MeCN, 85 °C, 3 h, R=H (60 %), OMe (74 %), OBn (70 %); b) pyrrolidine, MeCN, 0° C, 3 h, R=H (87%, d.r. 5:1), OMe (90%, d.r. 4:1), OBn (91%, d.r. 4:1); c) $NaBH_4$, EtOH, 0°C, 3 h, R=H (73%), OMe (71%), OBn (78%).

An additional synthetic route to clavilactone B features a sequential samarium-mediated radical cyclization−fragmentation of an indanone derivative, which provides rapid access to a 10-membered carbocyclic motif fused to an aromatic ring.[145] The approach would provide an alternative to the RCM-based routes that have been successfully developed so far to synthesize this class of attractive natural product.

2.6 LACTAMS

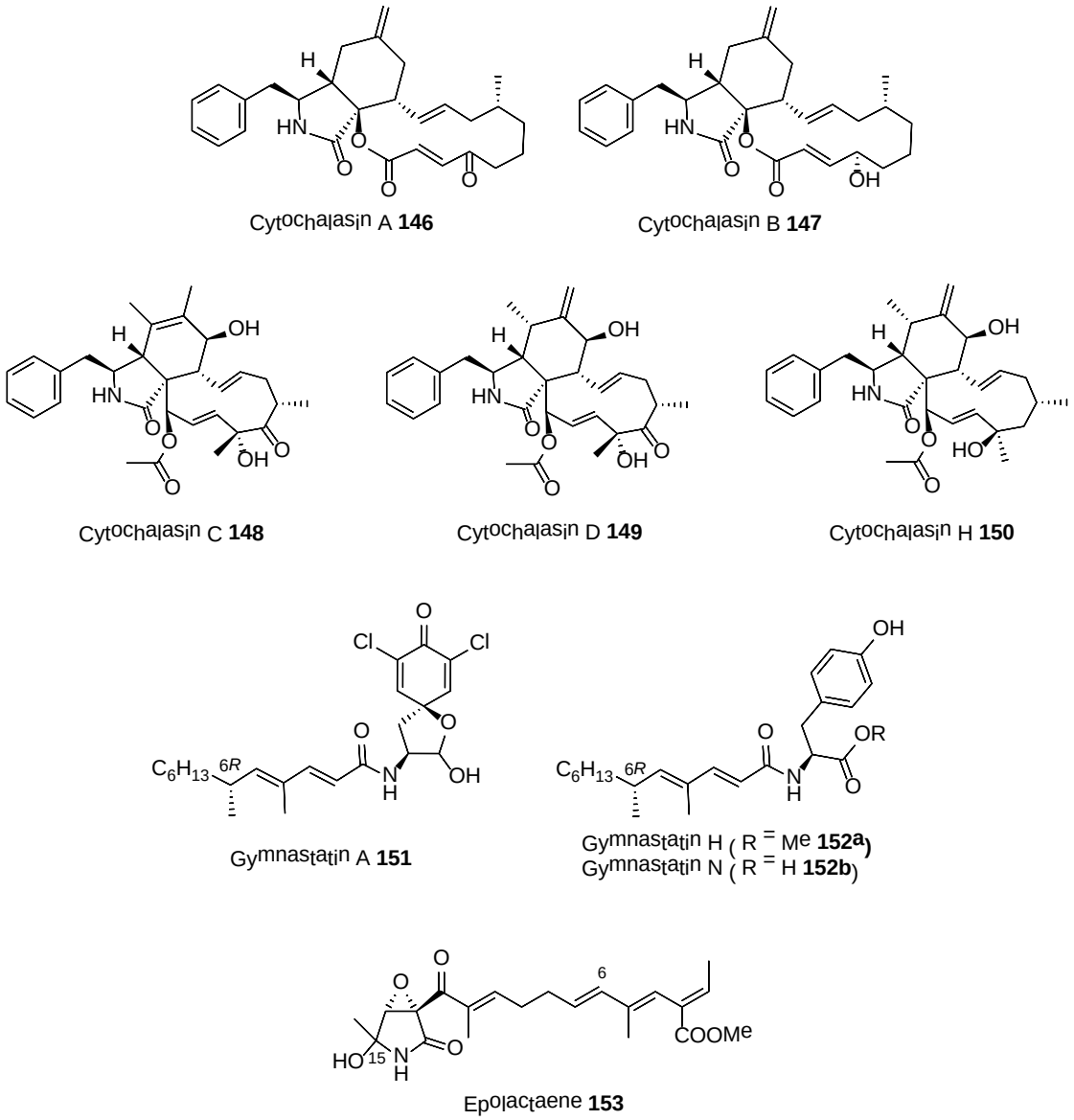


Figure 8 *Chemical structures of the discussed lactams*

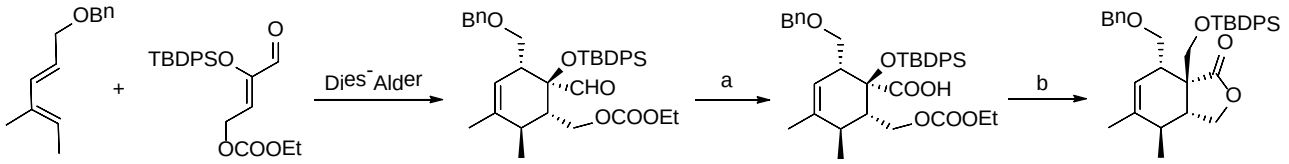
2.6.1 *Cytochalasins (146-150)*

Cytochalasins are fungal metabolites that have the ability to bind to actin filaments and inhibit the polymerization and elongation of actin. As a result of the inhibition of actin polymerization, cytochalasins can change cellular morphology, inhibit cellular processes, such as cell division, and even cause cells to undergo apoptosis.[146] The structural series is defined by a largely conserved rigid bicyclic isoindolone core that is fused to a macrocycle (**146-150** Figure 8). This last structural component varies widely within cytochalasins and seems to play an important role in the determination of biological activity. For example, cytochalasin B is an inhibitor of the formation of actin filaments, while the synthetic 11-membered macrocarbocyclic cytochalasin L has been reported to act as an inhibitor of HIV protease. Cytochalasins can also have an effect on other aspects of biological processes unrelated to actin polymerization. For example, cytochalasin A and cytochalasin B can also inhibit the transport of monosaccharides

across the cell membrane, cytochalasin H has been found to regulate plant growth, cytochalasin D inhibits protein synthesis and cytochalasin E prevents angiogenesis.

The complex structures and the extraordinary range of biological activity displayed by cytochalasans have stimulated many total synthesis programs. Since the synthesis of these challenging mycotoxins has been reviewed comprehensively by Hertweck and covers the literature up to 2009, we will only provide a short summary of the main syntheses proposed and the more recent updates.[147]

The first total synthesis of the 14-membered macrolactone, cytochalasin B, by G. Stork and co-workers[148] involves an intramolecular [4+2] cycloaddition as the key step. Alternative approaches in which the isoindolone core is prepared first have been proposed. In this context, Trost and co-workers developed a straightforward Pd-catalyzed synthesis to 11-membered cytochalasans, such as aspochalasin B.[149] Haidle and Meyers, however, established a convergent and highly modular route in order to provide a generally applicable synthetic platform for the preparation of cytochalasans with varying ring size and substitutions. They synthesized the 14-membered cytochalasin B and the 11-membered cytochalasin L-696,474. As in the above-mentioned cases, the synthesis starts with the preparation of the isoindolone, albeit by an alternative intramolecular Diels–Alder reaction.[150] Loh *et al.* have very recently proposed the synthesis of a key intermediate to the synthesis of cytochalsins which uses a Lewis acid catalyzed intermolecular Diels-Alder reaction and multi-functionalized diene and *Z*-enals to construct six-membered ring systems (Scheme 42).[151]



Scheme 42 *Loh's synthesis*: a) $NaClO_2$, NaH_2PO_4, *t*-BuOH, alkene (70%); b) i. $TMSCHN_2$, THF-MeOH, (71%); ii. LiOH, EtOH-H_2O (65%).

The cytochalasan scaffold is generally reduced to two principal subunits, the isoindolone core and a larger macrocyclic part, in all the above synthetic approaches.

2.6.2 *Gymnastatins (151,152)*

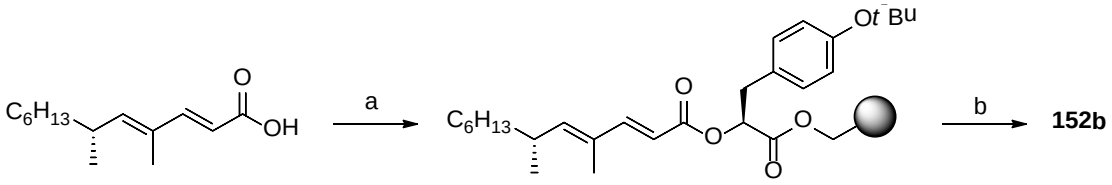
Gymnastatin A (**151** Figure 8) is a hemiacetal-type natural product, isolated from the strain of *Gymnescella dankaliensis*, but originally separated from the sponge *Halichondria japonica*, together with other gymnastatins.[152] Gymnastatins have been reported to exhibit significant cytotoxicity against cultured P388 cells. Several members of the gymnastatin family have shown protein kinase inhibitory activity.[153] Accordingly, their significant bioactivity and unique structure have meant that several groups have successfully developed synthetic investigations.

This class of fungal derived natural product contains a 4,6-dimethyl-dodecadien-2*E*,4*E*-oic acid unit connected to a tyrosine unit through an amide linkage. The tyrosine unit can have various degrees of oxygenation, halogenation, cyclisation and esterification, as found in gymnastatin A to H from *Gymnastella dankaliensis* (**151**, **152** Figure 8). These compounds have been reported to have antibacterial and anti-tumor activity.

The total synthesis of gymnastatin A [154], gymnastatin H[152] and gymnastatin I[155] have led to the determination of their absolute stereochemistry. It currently appears that all of these compounds have a (6*R*) configuration at the 4,6-dimethyl-dodecadien-2*E*,4*E*-oic acid unit.

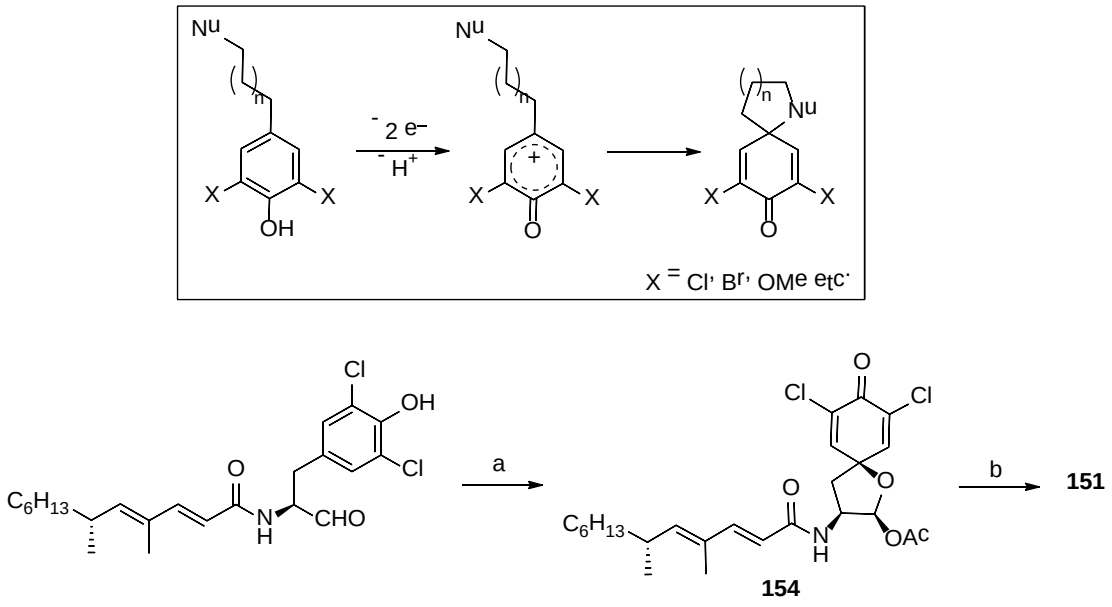
The first total synthesis of a novel, potent cytotoxic metabolite gymnastatin A was accomplished, in 2000, via the

oxidative cyclization of a 3,5-dichlorotyrosine derivative.[154] In 2004, Poohn *et al.* performed the total synthesis of gymnostatin N (Scheme 43).[156] Four stereoisomers were synthesized, but none of them matched natural gymnostatin N, which has proven to be a mixture of two stereoisomers, as demonstrated by the same authors.



Scheme 43 *Synthesis of gymnastatin N*: a) Wang resin-bound L-Tyr(t-Bu), PyBOP, HOBt, diisopropylethylamine, anhydrous DMA, rt, 18 h; b) TFA-DCM 1:1, rt, 2 h (93% from step a).

A different and elegant approach to gymnastatin A was proposed by Nishiyama and colleagues and occurs via the anodic oxidation of the corresponding phenols, which enabled the synthesis of spiroisoxazoline to be carried out (Scheme 44). The construction of spiro compounds that bear a hemiacetal moiety and the synthesis of gymnastatin A were achieved successfully.[157] The anodic oxidation of the substrate was performed in AcOH and gave the spirodienone compound. In the final step, the hydrolysis of the acetoxy ester in **154** was carried out giving gymnostatin A.

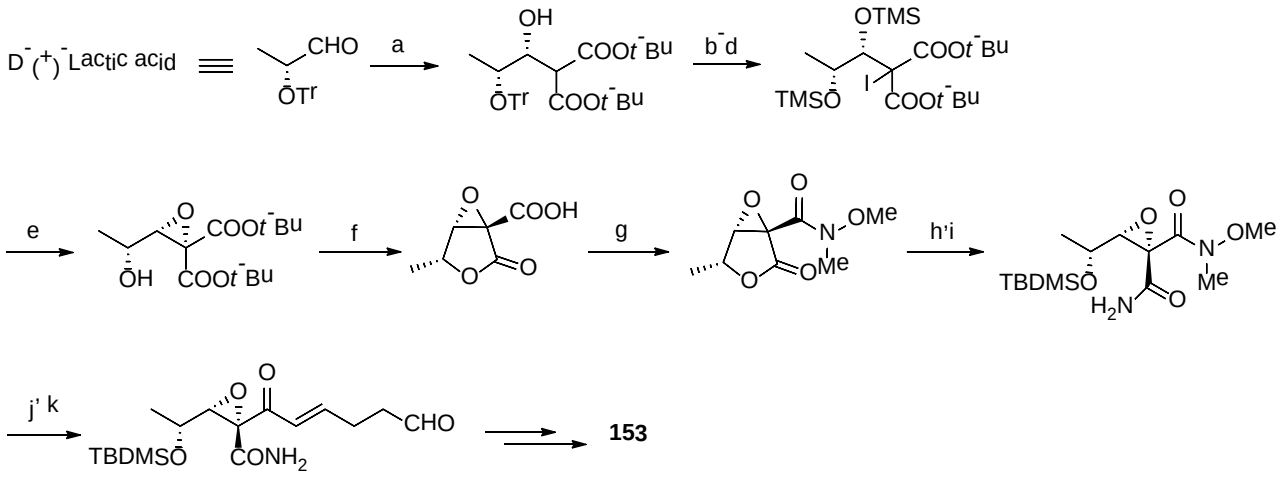


Scheme 44 *Nishiyama's synthesis of gymnostatin A*: a) anodic oxidation; b) AcOH, cat. H_2SO_4 aq., 50 °C (84%).

The asymmetric synthesis of gymnastatin H was achieved using the photoisomerization of a conjugated ester to its β,γ-unsaturated isomer and is in line with environmentally-friendly and more eco-compatible methods. The protonation onto one of the two diastereotopic faces proceeded well giving very high yields and selectivities thanks to the use of 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose as a chiral alkoxy group. Moreover, the configuration of the C-6 center of the target molecule was controlled using this method.[158] The total synthesis of (6*R*)-gymnastatin H was achieved in 14 steps and in a 4.3% overall yield via the highly diastereoselective photodeconjugation of a diacetone D-glucose ester, as the key step (de >95%).

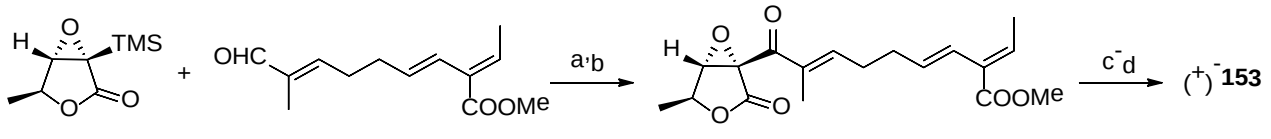
2.6.3 *Epolactaene (153)*

Epolactaene (**153** Figure 8) was isolated as a diastereomeric mixture, at the C-15 position (ca. 5:1 ratio), from the culture broth of *Penicillium* sp. BM 1689-P in 1995 by Osada *et al.*[159] The compound shows potent neurite outgrowth activity in the human neuroblastoma cell line SH-SY5Y.[160] The structure of **153** was deduced by Osada using extensive NMR studies including ^{1}H-^{1}H COSY and HMBC. However, the initial structural assignment did not allow the absolute stereochemistry of the epoxy moiety to be determined, although it did establish the (*E*,*E*,*E*) geometry of the conjugated triene and the (*E*) configuration of the unsaturated ketone. In 1998, Marumoto *et al.* described the asymmetric total synthesis of (+)-epolactaene using a convergent approach starting from D-(+)-lactic acid, a C6 unit, and the Wittig reagent (Scheme 45), which was followed by cyclization to form the lactam ring.[161]



Scheme 45 *Marumoto's asymmetric synthesis of (+)-epolactaene*: a) i. $ZnCl_2$, ii. $LiCH(CO_2$-*t*-$Bu)_2$, THF, -78 °C (53%); b) CF_3CO_2H, DCM, 0 °C (80%); c) Me_3SiCl, imidazole, DMF, 0 °C (94%); d) i. LHMDS, ii. I_2, -78 °C; e) TBAF, THF, -45 to -15 °C (52% two steps); f) HCO_2H, rt; g) Me_2NH,HCl, PyBOP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C (69% two steps; h) NH_3, MeOH, rt; i) TBDMSCl, imidazole, DMF, 0 °C to rt (93% two steps); j) (*Z*)-$Br(CH_3)CdCH$- $(CH_2)_3OH$, *t*-BuLi, THF, -78 °C (83%); k) Dess-Martin reagent, DCM, rt (81%).

The total synthesis of **153** was carried out by Kobayashi *et al.* in 2003 and relied on an aldol-type condensation of the epoxylactone which occurred via a two-step procedure from the chiral trimethylsilyl epoxylactone which is derived from L-xylose.[162] The same synthetic approach was more recently applied by Negishi *et al.* in 2006 (Scheme 46).[163] In this case, the chiral epoxy lactone was prepared from (*S*)-3-butyn-2-ol and the synthesis of (+)-epolactaene was performed using a linear approach consisting of 14 steps.



Scheme 46 *Negishi's synthesis of (+)-epolactaene*: a) i. TBAF, THF/hexane, ii. HF, MeCN (39% two steps); b) TFAA, DMSO, Et_3N, DCM (85%); c) NH_3, MeOH; d) Dess-Martin reagent, DCM (53% two steps).

Even more recently, a second generation approach to (+)-epolactaene was proposed which makes use of the highly stereoselective synthesis of the epoxy-γ-lactam moiety via an *E*-selective Horner-Wadsworth–Emmons reaction and the

diastereoselective epoxidation of the allyl diol.[164]

2.7 EPOXIDES

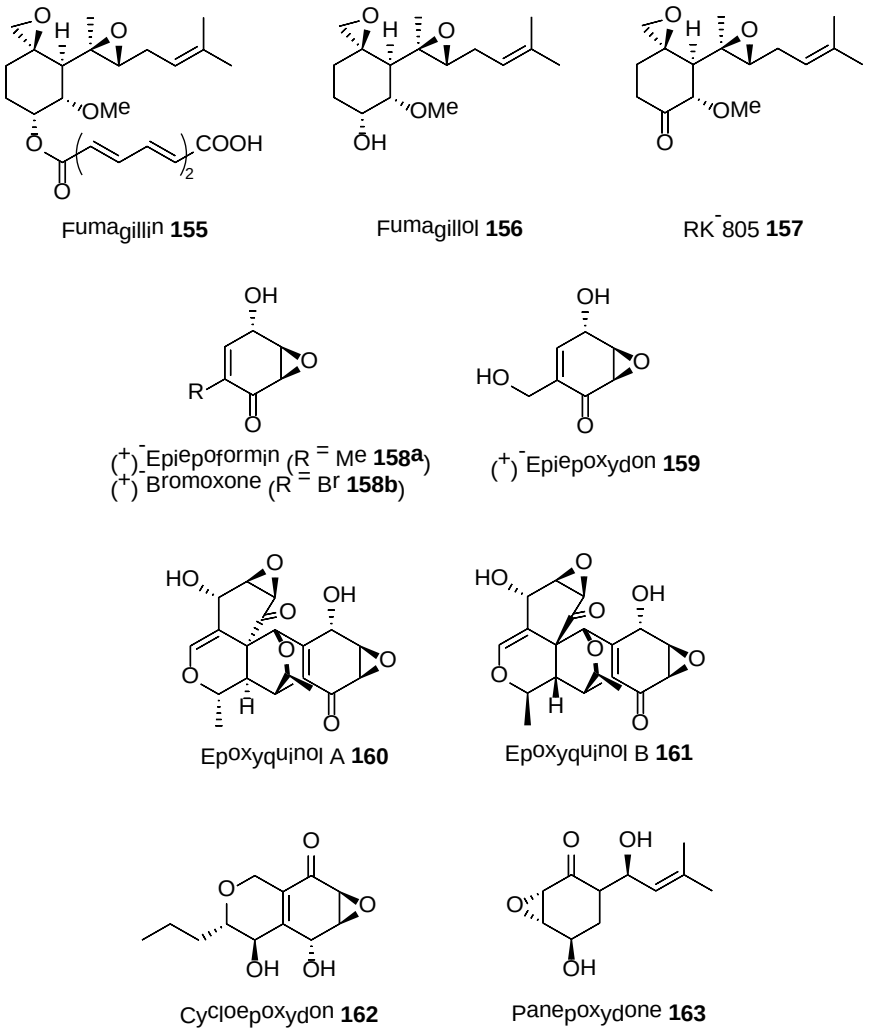


Figure 9 *Chemical structures of the discussed epoxides*

2.7.1 *Fumagillin (155), fumagillol (156) and RK-805 (157)*

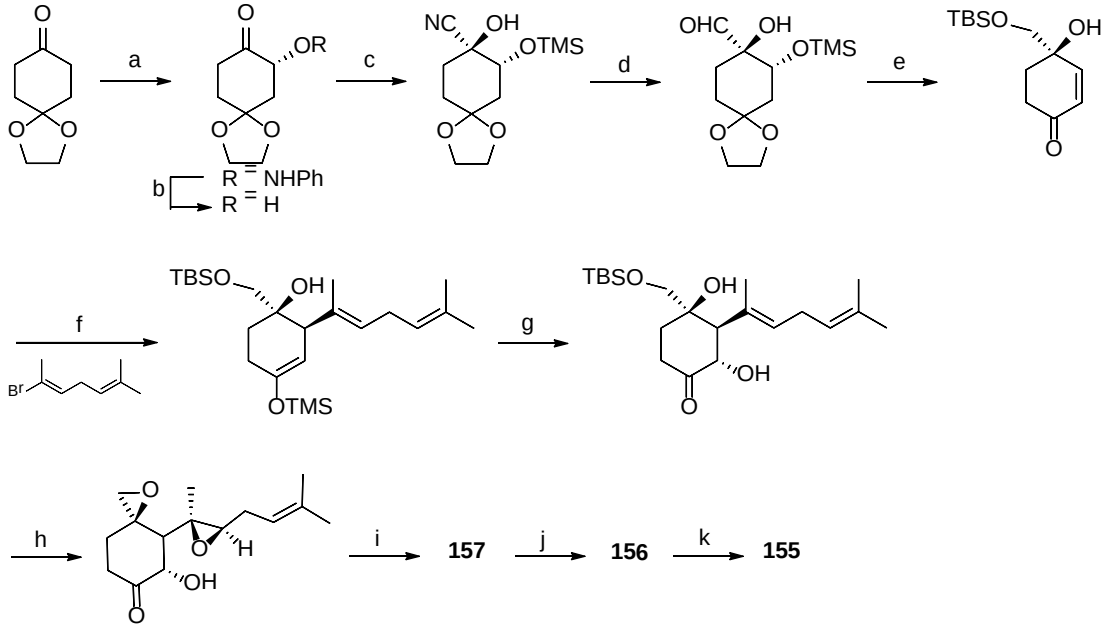
Fumagillin (**155** Figure 9) is an antibiotic originally isolated from the microbial organism, *Aspergillus fumigatus*, while also produced by *Aspergillus* sp, *A. flavus* and *parasiticus*.[3]

Concerning its biosynthetic origin, fumagillin derives from both the terpene pathway and the acetate route.[3] It was first described as an antiparasitic[165] and carcinolytic agent.[166] More recently, it has been discovered that fumagillin can block blood vessel formation by binding to the enzyme methionine aminopeptidase and, for this reason, the compound, together with its semisynthetic derivatives, are investigated as an angiogenesis inhibitor in the treatment of cancer [167] (for recent reviews see ref 192 [168]). Some fumargillin analogues have also been evaluated in human cancer clinical trials.[3]

The intriguing biological activities of fumagillin and its derivatives have stimulated the interest of several groups. In fact, many comprehensive reviews have been published on its synthesis since 2003 and up to 2012.[169] The best is

surely the one written by Yamaguchi and Hayashi in 2010.[169c] Herein, we would like to highlight a few synthetic aspects of this pivotal molecule.

Four racemic syntheses, including Corey's first excellent total syntheses of fumagillin, have been reported.[170] Diastereoselective syntheses of fumagillin using chiral auxiliaries have been reported by Sorensen.[171] A more flexible approach to the fumagillin core, using a diastereoselective asymmetric catalytic total synthesis and the proline-mediated α-aminoxylation of carbonyl compounds as the key step, was proposed in 2006 by Hayashi *et al*. (Scheme 47).[172]. In summary, the reaction proceeds via the following principal transformations: 1) the highly diastereoselective formation of bis(trimethylsilyl ether) cyanide involving kinetic discrimination; 2) a diastereoselective Michael reaction using vinyl zincate; 3) a stereoselective double epoxidation catalyzed by $VO(OiPr)_3$ at low temperature; 4) an alkylative deprotection of an oxime.



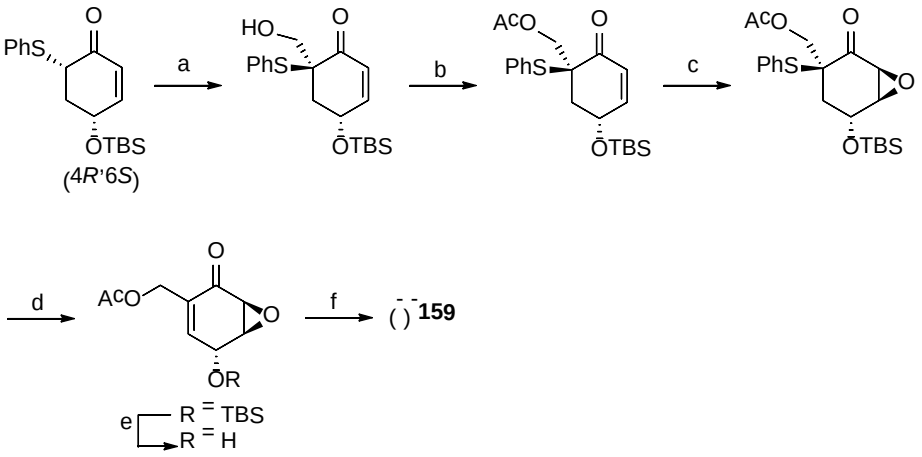
Scheme 47 *Hayashi's synthesis of fumagillin*: a) *L*-prolin (10%), Ph-N=O, DMF 0° C, 24 h (93%, > 99% ee); b) Pd/C, H_2 (90%); c) TMSCN, cat. Et_3N, DCM (68% yield, > 95:5 dr); d) DIBAL-H, Et_2O, - 60 °C to -30 °C (72%); e) i. DIBAL-H, DCM, ii. Amberlyst-15, THF, 60 °C, iii. TBSCl, Et_3N cat. DMAP, DCM (57% over 3 steps); f) *t*-BuLi, Me_2N_2, THF, -78 °C to -40 °C, 2h then TMSCl, Et_3N -40 °C to -20 °C, 1 h (61 %, > 95:5 dr); g) i. DMD, MeOH, -90 °C, ii. TBAF, THF (74% yield, 95:5); h) i. cat $Vo(acac)_2$, TBHP, DCM, ii. K_2CO_3, MeOH (75%, 95:5 dr); i) MeI, Ag_2O, MeCN; j) K-selectride (94%, > 95:5 dr); k) see ref .172

2.7.2 *Epiepoxydon (159), Epiepoformin (158a) and Bromoxone (158b)*

Epiepoxydon (**159** Figure 9) and related compounds are well known as typical oxygenated cyclohexenones with remarkable biological activiy. Epiepoxydon was isolated from the culture broth of an unidentified fungus separated from a diseased crapemyrtle leaf by Nagasawa and co-workers in 1978.[173] The acetate of bromoxone (**158b** Figure 9) shows potent antitumor activity against P388 cells *in vitro*.[174] Several methods for their synthesis have already been reported.[175] In 2003, Tachihara and Kitahara described novel syntheses of epiepoformin, epiepoxydon and bromoxone using a common chiral building block; ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate.[175b] A simple enzyme mediated strategy to access chiral building blocks for the synthesis of a range of biologically active epoxyquinone natural products from readily available starting materials was proposed by Metha and coworkers.[176]

The levorotatory enantiomer of epiepoxidon has recently been prepared. The approach relies on the initial

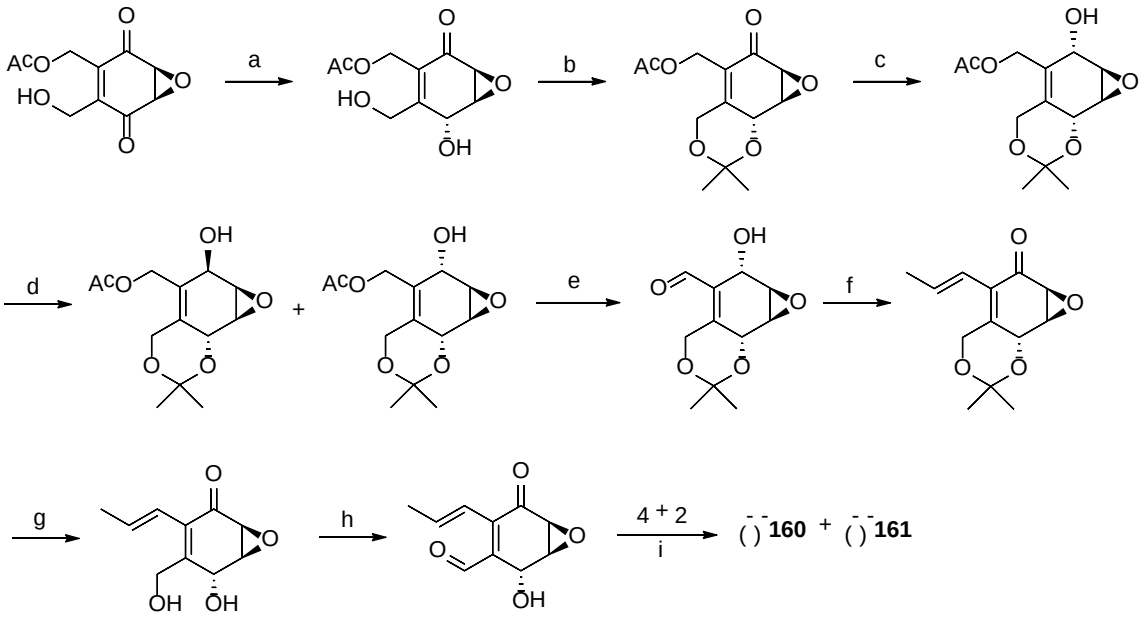
desymmetrization of *p*-methoxyphenol, followed by an enzymatic resolution that separately provides the two enantiomers of a key synthon.[177] The first synthesis of (-)-epiepoxydon was then accomplished from a simple precursor, in six steps with a 40 % overall yields (Scheme 48).



Scheme 48 *Synthesis of (-)-epiepoxydon*: a) HCHO, *t*-BuOK (88%); b) Ac_2O, Py (99%); c) *t*-BuOOH, Triton B (76%); d) MCPBA, $CHCl_3$; e) Et_3N, HF; f) CALB, *i*-Pr_2O (75%).

2.7.3 *Epoxyquinols (160,161)*

Of the members of the family of natural compounds bearing the epoxyquinol moiety, shown in Figure 9, epoxyquinol A and B are worthy of mention. They were synthesized by Metha *et al.* [178] from the readily available Diels–Alder adduct between cyclopentadiene and *p*-benzoquinone (Scheme 49).



Scheme 49 *Metha's synthesis of epoxyquinols*: a) DIBAL-H, THF, -78°C (74%); b) Dess-Martin periodinane, PPTS, acetone, rt (89%); c) $NaBH_4$, $CeCl_3/H_2O$, MeOH, 0°C (86%); d) K_2CO_3, MeOH, 0°C (74%); e) TEMPO, O_2, CuCl, DMF (76%); f) $C_2H_5PPh_3Br$, n-BuLi, THF, 0 °C; g) Amberlyst 15, MeOH, rt (79%); h) TEMPO, O_2 , CuCl, DMF, rt; i) neat, 30 °C, 8 h, (**160** 48% and (**161** 18%).

Porco performed the synthesis of epoxyquinols A and B and a number of related compounds using [4 + 2] and [4 + 4]

dimerizations of 2H-pyran epoxyquinol monomers. Modifications to 2H-pyran precursors have been explored and include the alteration of epoxy alcohol and diene stereochemistry.[179] An asymmetric total synthesis of the novel epoxyquinol natural product (+)-panepophenanthrin has been accomplished following this synthetic approach and using a biomimetic Diels–Alder dimerisation is the key step. The key monomeric precursor was assembled via the efficient Stille cross coupling of two readily available building blocks that, upon standing, underwent a diastereospecific dimerization cascade in excellent yield.[180]

2.7.4 *Cycloepoxydon (162)*

Cycloepoxydon (**157** Figure 9) has been isolated from a deuteromycete strain [181] and has been shown to inhibit the activation of NF-κB, an inducible, ubiquitous transcription factor that regulates the expression of various cellular genes involved in immune and inflammation responses and apoptosis.[182] Metha carried out the enantioselective total synthesis of (-)-cycloepoxydon using a readily available Diels-Alder adduct of cyclopentadiene and *p*-benzoquinone.[183].

2.7.5 *Panepoxydone (163)*

Structurally related to cycliepoxydone, panepoxydone (**163** Figure 9) has been isolated from basidiomycete *conchatus* [182] and reported to exhibit potent NF-B inhibitory activity.[184] Efficient strategies for producing, these and other, congeners via total synthesis have been proposed. In 2000, Wood and colleagues described the first total synthesis of panepoxydone along with the correction of the absolute configuration originally assigned.[185] Structure-activity relationship studies of this class of compound have also been reported.[186]

3. Conclusion

Fungi have always been a rich source of effective drugs and are still an important source for the identification of new pharmacological leads today. Renewed scientific interest in the drug discovery of fungi-derived natural products is evident in a huge number of publications in this field. As a consequence, new approaches to the identification, characterization and resupply of natural products are highly desirable. These may address some of the challenges related to the development of fungi-based therapeutics. Resupply from the original fungal species is often too unfeasible to meet market demands upon commercialization of a natural product. Moreover, alternative resupply approaches, which relying on biotechnological production or chemical synthesis, are being developed. In this review, we have demonstrated that total chemical synthesis is an effective resupply strategy. As an alternative, the improvement of knowledge on fungi biosynthetic pathways will facilitate the development of more efficient genetic engineering strategies and tools. Research trends clearly indicate that natural products will be among the most important sources of new drugs in the future. However, their full potential will only be realized through a highly integrated interdisciplinary approach made possible by recent advances in technology and knowledge.

LIST OF ABBREVIATIONS

Acac = Acetylacetonato

AcOH = Acetic acid

AIBN = 2,2′-Azobis(2-methylpropionitrile)

Alloc = Allyloxycarbonyl

(S)-BINAP = (S)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene

Bn = Benzyl

Boc = *tert*-Butoxycarbonyl

BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphonyl chloride

9-BBN = 9-Borabicyclo[3.3.1]nonane

CAN = Cerium Ammonium Nitrate

CALB = Candida Antarctica Lipase B

Cp = Pentamethylcyclopentadienyl

m-CPBA = *m*-Chloroperbenzoic acid

(+)-CSA = (+)-10-Camphorosulfonic acid

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC = *N*,*N*′-Dicyclohexylcarbodiimide

DCE = Dichloroethane

DCM = Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL-H = Diisobutylaluminium hydride

DIPEA = *N*,*N*-Diisopropylethylamine

L-DIPT = (+)-Diisopropyl L-tartrate

DMA = *N*,*N*-Dimethylacetamide

DMAP = 4-Dimethylaminopyridine

DMAPP = Dimethyallyl pyrophosphate

DMD = 5,6-Dimethyl-1H-benzimidazole

DMDO = Dimethyldioxirane

DMF = *N*,*N*-dimethylformamide

DMSO = Dimethyl sulfoxide

EDC HCl = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride

HATU = 2-(1-H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium

HMDS = Bis(trimethylsilyl)amide

HOAt = 1-Hydroxy-7-azabenzotriazole

HOBt = 1-Hydroxybenzotriazole

IBX = 2-Iodoxybenzoic acid

LDA = Lithium diisopropylamide

MNBA = 2-Methyl-6-nitrobenzoic anhydride

NBS = N-Bromosuccunimide

NMO = N-methylmorpholine-N-oxide

NMM = N-methylmorpholine

nor-AZADO = 9-Azanoradamantane-*N*-oxyl

MOMCl = Methoxymethyl chloride

PCC = Pyridinium chlorochromate

PDC = Pyridinium dichromate

PPTS = Pyridinium *p*-toluenesulfonate

Pyr = Pyridine

PyBOP = (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

TASF = Tris(dimethylamino)sulfur trimethylsilyl difluoride

TBAA = Tetrabutylammonium acetate

TBAB = Tetrabutylammonium bromide

TBAF = Tetrabutylammonium fluoride

TBAOH = Tetrabutylammonium hydroxide

TBDMSCl = *tert*-Butyldimethylsilyl chloride

TBDPS = *tert*-Butyldiphenylsilyl

TBHP = *tert*-Butyl hydroperoxide

TBS = *tert*-Butyldimethylsilyl

TEMPO = 2,2,6,6-Tetramethylpiperidin-1-yloxy

TESCl = Triethysilyl chloride

Tf = Triflate (trifluoromethanesulfonate)

TFA= Trifluoroacetic acid

TFAA = Trifluoroacetic anhydride

THF = Tetrahydrofuran

TIPSOTf = Triisopropylsilyl trifluoromethanesulfonate

TMEDA = *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

TMP = 2,2,6,6-Tetramethylpiperidine

TMSCHN2 = Trimethylsilyl diazomethane

TMSCN = Trimethylsilyl cyanide

TMSI = Trimethylsilyl iodide

TMSOTf = Trimethylsilyl trifluoromethanesulfonate

TPAP = Tetrapropylammonium perruthenate

Ts = Tosyl

TrSSSCl = Chloro(triphenylmethyl) trisulfane

SEMCl = 2-(Trimethylsilyl)ethoxymethyl chloride

WSCD = Water soluble carbodiimide

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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REFERENCES

[1] Nicoletti, R.; Fiorentino, A., Antitumor Metabolites of Fungi. *Curr. Bioact. Compd.* **2014,** *10* (4), 207-244.

[2] Evidente, A.; Kornienko, A.; Cimmino, A.; Andolfi, A.; Lefranc, F.; Mathieu, V.; Kiss, R., Fungal metabolites with anticancer activity. *Nat. Prod. Rep.* **2014,** *31* (5), 617-627.

[3] Kornienko, A.; Evidente, A.; Vurro, M.; Mathieu, V.; Cimmino, A.; Evidente, M.; van Otterlo, W. A. L.; Dasari, R.; Lefranc, F.; Kiss, R., Toward a Cancer Drug of Fungal Origin. *Med. Res. Rev.* **2015,** *35* (5), 937-967.

[4] Wang, L. W.; Zhang, Y. L.; Lin, F. C.; Hu, Y. Z.; Zhang, C. L., Natural Products with Antitumor Activity from Endophytic Fungi. *Mini-Reviews in Medicinal Chemistry* **2011,** *11* (12), 1056-1074.

[5] Kharwar, R. N.; Mishra, A.; Gond, S. K.; Stierle, A.; Stierle, D., Anticancer compounds derived from fungal endophytes: their importance and future challenges. *Natural Product Reports* **2011,** *28* (7), 1208-1228.

[6] Sears, J. E.; Boger, D. L., Total Synthesis of Vinblastine, Related Natural Products, and Key Analogues and Development of Inspired Methodology Suitable for the Systematic Study of Their Structure-Function Properties. *Acc. Chem. Res.* **2015,** *48* (3), 653-662.

[7] Alehashem, M. S.; Lim, C.-G.; Thomas, N. F., The radical cation mediated cleavage of catharanthine leading to the vinblastine type alkaloids: implications for total synthesis and drug design. *RSC Adv.* **2016,** *6* (22), 18002-18025.

[8] Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A., Plant antitumor agents. I. Isolation and structure of camtothecin, a novel alkaloidal leukemia and tumor inhibitor from Camptotheca acuminata. *J. Am. Chem. Soc.* **1966,** *88* (16), 3888-3890.

[9] Puri, S. C.; Verma, V.; Amna, T.; Qazi, G. N.; Spiteller, M., An Endophytic Fungus from Nothapodytes foetida that Produces Camptothecin. *J. Nat. Prod.* **2005,** *68* (12), 1717-1719.

[10] Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F., Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J. Biol. Chem.* **1985,** *260* (27), 14873-14878.

[11] (a) Du, W., Towards new anticancer drugs: a decade of advances in synthesis of camptothecins and related alkaloids. *Tetrahedron* **2003,** *59* (44), 8649-8687; (b) Thomas, C. J.; Rahier, N. J.; Hecht, S. M., Camptothecin: current perspectives. *Bioorg Med Chem* **2004,** *12* (7), 1585-1604; (c) Driver, R. W.; Yang, L.-X., Synthesis and pharmacology of new camptothecin drugs. *Mini Rev Med Chem* **2005,** *5* (5), 425-439; (d) Li, Q.-Y.; Zu, Y.-G.; Shi, R.-Z.; Yao, L.-P., Review camptothecin: current perspectives. *Curr Med Chem* **2006,** *13* (17), 2021-2039; (e) Liew, S. T.; Yang, L.-X., Design, synthesis and development of novel camptothecin drugs. *Curr. Pharm. Des.* **2008,** *14* (11), 1078-1097.

[12] El-Gendy, B. E.-D. M.; Rateb, M. E., Antibacterial activity of diketopiperazines isolated from a marine fungus using t-butoxycarbonyl group as a simple tool for purification. *Bioorg. Med. Chem. Lett.* **2015,** *25* (16), 3125-3128.

[13] Hayashi, Y.; Yamazaki-Nakamura, Y.; Yakushiji, F., Medicinal chemistry and chemical biology of diketopiperazine-type antimicrotubule and vascular-disrupting agents. *Chem. Pharm. Bull.* **2013,** *61* (9), 889-901.

[14] Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; Kiso, Y., Total Synthesis of Anti-microtubule Diketopiperazine Derivatives: Phenylahistin and Aurantiamine. *J. Org. Chem.* **2000,** *65* (24), 8402-8405.

[15] Liao, S.; Qin, X.; Li, D.; Tu, Z.; Li, J.; Zhou, X.; Wang, J.; Yang, B.; Lin, X.; Liu, J.; Yang, X.; Liu, Y., Design and synthesis of novel soluble 2,5-diketopiperazine derivatives as potential anticancer agents. *Eur. J. Med. Chem.* **2014,** *83*, 236-244.

[16] Kanoh, K.; Kohno, S.; Asari, T.; Harada, T.; Katada, J.; Muramatsu, M.; Kawashima, H.; Sekiya, H.; Uno, I., (-)-Phenylahistin: a new mammalian cell cycle inhibitor produced by Aspergillus ustus. *Bioorg. Med. Chem. Lett.* **1997,** *7* (22), 2847-2852.

[17] Yamazaki, Y.; Tanaka, K.; Nicholson, B.; Deyanat-Yazdi, G.; Potts, B.; Yoshida, T.; Oda, A.; Kitagawa, T.; Orikasa, S.; Kiso, Y.; Yasui, H.; Akamatsu, M.; Chinen, T.; Usui, T.; Shinozaki, Y.; Yakushiji, F.; Miller, B. R.; Neuteboom, S.; Palladino, M.; Kanoh, K.; Lloyd, G. K.; Hayashi, Y., Synthesis and structure-activity relationship study of antimicrotubule agents phenylahistin derivatives with a didehydropiperazine-2,5-dione structure. *J. Med. Chem.* **2012,** *55* (3), 1056-1071.

[18] (a) Couladouros, E. A.; Magos, A. D., Total asymmetric synthesis of (-)-phenylahistin, (-)-aurantiamine and related compounds. Part I. *Mol. Diversity* **2005,** *9* (1-3), 99-109; (b) Couladouros, E. A.; Magos, A. D., Solid-phase total synthesis of (-)-phenylahistin and (-)-aurantiamine. Synthesis of a diverse dehydro-2,5-diketopiperazine library. Part II. *Mol. Diversity* **2005,** *9* (1-3), 111-121; (c) Shangguan, N.; Joullie, M. M., Total synthesis of isoroquefortine E and phenylahistin. *Tetrahedron Lett.* **2009,** *50* (49), 6755-6757.

[19] Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H., Tryprostatins A and B, novel mammalian cell cycle inhibitors produced by Aspergillus fumigatus. *J. Antibiot.* **1995,** *48* (11), 1382-1384.

[20] Wagger, J.; Svete, J.; Stanovnik, B., Synthesis of unsaturated tryprostatin B analogues and determination of their enantiomeric purity with (S)-1-benzyl-6-methylpiperazine-2,5-dione. *Synthesis* **2008,** (9), 1436-1442.

[21] Maison, W., Synthesis of 1,4-diazabicyclo[X.Y.O]alkanes; scaffolds of dipeptide mimetics and proline derived natural products. *Targets Heterocycl. Syst.* **2005,** *9*, 87-113.

[22] Van, T. N.; Claes, P.; De Kimpe, N., Synthesis of functionalized diketopiperazines as Cyclotryprostatin and Tryprostatin. *Synlett* **2013,** *24* (8), 1006-1010.

[23] Jain, H. D.; Zhang, C.; Zhou, S.; Zhou, H.; Ma, J.; Liu, X.; Liao, X.; Deveau, A. M.; Dieckhaus, C. M.; Johnson, M. A.; Smith, K. S.; Macdonald, T. L.; Kakeya, H.; Osada, H.; Cook, J. M., Synthesis and structure-activity relationship studies on tryprostatin A, an inhibitor of breast cancer resistance protein. *Bioorg. Med. Chem.* **2008,** *16* (8), 4626-4651.
[24] Cardoso, A. S. P.; Marques, M. M. B.; Srinivasan, N.; Prabhakar, S.; Lobo, A. M.; Rzepa, H. S., Studies in sigmatropic rearrangements of N-prenylindole derivatives - a formal enantiomerically pure synthesis of tryprostatin B. *Org. Biomol. Chem.* **2006,** *4* (21), 3966-3972.
[25] Yamakawa, T.; Ideue, E.; Iwaki, Y.; Sato, A.; Tokuyama, H.; Shimokawa, J.; Fukuyama, T., Total synthesis of tryprostatin A and B. *Tetrahedron* **2011,** *67* (35), 6547-6560.
[26] Yamakawa, T.; Ideue, E.; Shimokawa, J.; Fukuyama, T., Total Synthesis of Tryprostatins A and B. *Angew. Chem., Int. Ed.* **2010,** *49* (48), 9262-9265, S9262/1-S9262/86.
[27] (a) Hino, T.; Nakagawa, M., Total synthesis of fumitremorgins and verruculogens. *Heterocycles* **1997,** *46*, 673-704; (b) Wang, H.; Ganesan, A., Concise synthesis of the cell cycle inhibitor demethoxyfumitremorgin C. *Tetrahedron Lett.* **1997,** *38* (24), 4327-4328.
[28] Ren, H.; Cao, X.; Wang, Q.; Xu, C., Antitumor metabolites from fungus Aspergillus sydowi D 2-6. *Zhongguo Yaoxue Zazhi (Beijing, China)* **2011,** *46* (8), 569-575.
[29] Wang, H.; Ganesan, A., The N-Acyliminium Pictet-Spengler Condensation as a Multicomponent Combinatorial Reaction on Solid Phase and Its Application to the Synthesis of Demethoxyfumitremorgin C Analogues. *Org. Lett.* **1999,** *1* (10), 1647-1649.
[30] Bailey, P. D.; Cochrane, P. J.; Lorenz, K.; Collier, I. D.; Pearson, D. P. J.; Rosair, G. M., A concise, efficient route to fumitremorgins. *Tetrahedron Lett.* **2001,** *42* (1), 113-115.
[31] Jiang, D.; Xu, Z.; Jia, Y., Mg(ClO4)2-Catalyzed intramolecular allylic amination: application to the total synthesis of demethoxyfumitremorgin C. *Tetrahedron* **2012,** *68* (22), 4225-4232.
[32] Arai, K.; Kimura, K.; Mushiroda, T.; Yamamoto, Y., Structures of fructigenines A and B, new alkaloids isolated from Penicillium fructigenum Takeuchi. *Chem. Pharm. Bull.* **1989,** *37* (11), 2937-2939.
[33] Karwowski, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B., 5-N-Acetylardeemin, a novel heterocyclic compound which reverses multiple drug resistance in tumor cells. I. Taxonomy and fermentation of the producing organism and biological activity. *J. Antibiot.* **1993,** *46* (3), 374-379.
[34] He, B.; Song, H.; Du, Y.; Qin, Y., Total Synthesis of (-)-Ardeemin. *J. Org. Chem.* **2009,** *74* (1), 298-304.
[35] Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Alvarez, M., Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]indole. *Chem. - Eur. J.* **2011,** *17* (5), 1388-1408.
[36] Takiguchi, S.; Iizuka, T.; Kumakura, Y.-s.; Murasaki, K.; Ban, N.; Higuchi, K.; Kawasaki, T., Total Syntheses of (-)-Fructigenine A and (-)-5-N-Acetylardeemin. *J. Org. Chem.* **2010,** *75* (4), 1126-1131.
[37] Wang, Y.; Kong, C.; Du, Y.; Song, H.; Zhang, D.; Qin, Y., Silver-promoted Friedel-Crafts reaction: concise total synthesis of (-)-ardeemin, (-)-acetylardeemin and (-)-formylardeemin. *Org. Biomol. Chem.* **2012,** *10* (14), 2793-2797.
[38] (a) Sunazuka, T.; Hirose, T.; Omura, S., Efficient Total Synthesis of Novel Bioactive Microbial Metabolites. *Acc. Chem. Res.* **2008,** *41* (2), 302-314; (b) Ideguchi, T.; Yamada, T.; Shirahata, T.; Hirose, T.; Sugawara, A.; Kobayashi, Y.; Omura, S.; Sunazuka, T., Asymmetric Total Synthesis of Neoxaline. *J. Am. Chem. Soc.* **2013,** *135* (34), 12568-12571; (c) Yamada, T.; Ideguchi-Matsushita, T.; Hirose, T.; Shirahata, T.; Hokari, R.; Ishiyama, A.; Iwatsuki, M.; Sugawara, A.; Kobayashi, Y.; Otoguro, K.; Omura, S.; Sunazuka, T., Asymmetric Total Synthesis of Indole Alkaloids Containing an Indoline Spiroaminal Framework. *Chem. - Eur. J.* **2015,** *21* (33), 11855-11864.
[39] (a) DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F.-L.; Overman, L. E., General Approach for Preparing Epidithiodioxopiperazines from Trioxopiperazine Precursors: Enantioselective Total Syntheses of (+)- and (-)-Gliocladine C, (+)-Leptosin D, (+)-T988C, (+)-Bionectin A, and (+)-Gliocladin A. *J. Am. Chem. Soc.* **2013,** *135* (10), 4117-4128; (b) Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi, M., Synthesis and anticancer activity of epipolythiodiketopiperazine alkaloids. *Chem. Sci.* **2013,** *4* (4), 1646-1657; (c) Kim, J.; Movassaghi, M., Biogenetically-Inspired Total Synthesis of Epidithiodiketopiperazines and Related Alkaloids. *Acc. Chem. Res.* **2015,** *48* (4), 1159-1171.
[40] Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguere, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A., Synthesis and Biological Evaluation of Epidithio-, Epitetrathio-, and bis-(Methylthio)diketopiperazines: Synthetic Methodology, Enantioselective Total Synthesis of Epicoccin G, 8,8'-epi-ent-Rostratin B, Gliotoxin, Gliotoxin G, Emethallicin E, and Haematocin and Discovery of New Antiviral and Antimalarial Agents. *J. Am. Chem. Soc.* **2012,** *134* (41), 17320-17332.
[41] (a) Kishi, Y.; Fukuyama, T.; Nakatsuka, S., New method for the synthesis of epidithiodiketopiperazines. *J. Amer. Chem. Soc.* **1973,** *95* (19), 6490-6492; (b) Fukuyama, T.; Kishi, Y., A total synthesis of gliotoxin. *J. Am. Chem. Soc.* **1976,** *98* (21), 6723-6724; (c) Fukuyama, T.; Nakatsuka, S.; Kishi, Y., Total synthesis of gliotoxin, dehydrogliotoxin and hyalodendrin. *Tetrahedron* **1981,** *37* (11), 2045-2078.
[42] Kim, J.; Movassaghi, M., Biogenetically inspired syntheses of alkaloid natural products. *Chem. Soc. Rev.* **2009,** *38* (11), 3035-3050.

[43] Kim, J.; Ashenhurst, J. A.; Movassaghi, M., Total Synthesis of (+)-11,11'-Dideoxyverticillin A. *Science (Washington, DC, U. S.)* **2009,** *324* (5924), 238-241.
[44] (a) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M., Total Synthesis of (+)-Chaetocin and its Analogues: Their Histone Methyltransferase G9a Inhibitory Activity. *J. Am. Chem. Soc.* **2010,** *132* (12), 4078-4079; (b) Kim, J.; Movassaghi, M., General Approach to Epipolythiodiketopiperazine Alkaloids: Total Synthesis of (+)-Chaetocins A and C and (+)-12,12'-Dideoxychetracin A. *J. Am. Chem. Soc.* **2010,** *132* (41), 14376-14378.
[45] (a) Miller, S. J., Total Chemical Synthesis Peers into the Biosynthetic Black Box. *Science (Washington, DC, U. S.)* **2009,** *324* (5924), 186-187; (b) Sodeoka, M.; Dodo, K.; Teng, Y.; Iuchi, K.; Hamashima, Y.; Iwasa, E.; Fujishiro, S., Synthesis and biological activities of chaetocin and its derivatives. *Pure Appl. Chem.* **2012,** *84* (6), 1369-1378.
[46] (a) Wang, L.; Clive, D. L. J., Synthetic studies related to MPC1001: formation of a model epidithiodiketopiperazine. *Tetrahedron Lett.* **2012,** *53* (12), 1504-1506; (b) Kurogi, T.; Okaya, S.; Fujiwara, H.; Okano, K.; Tokuyama, H., Total Synthesis of (+)-MPC1001B. *Angew. Chem., Int. Ed.* **2016,** *55* (1), 283-287.
[47] (a) Trost, B. M.; Osipov, M., Recent Advances on the Total Syntheses of Communesin Alkaloids and Perophoramidine. *Chem. - Eur. J.* **2015,** *21* (46), 16318-16343; (b) Zi, W.; Zuo, Z.; Ma, D., Intramolecular Dearomative Oxidative Coupling of Indoles: A Unified Strategy for the Total Synthesis of Indoline Alkaloids. *Acc. Chem. Res.* **2015,** *48* (3), 702-711.
[48] Lathrop, S. P.; Pompeo, M.; Chang, W.-T. T.; Movassaghi, M., Convergent and Biomimetic Enantioselective Total Synthesis of (-)-Communesin F. *J. Am. Chem. Soc.* **2016,** *138* (24), 7763-7769.
[49] Jiao, R. H.; Xu, S.; Liu, J. Y.; Ge, H. M.; Ding, H.; Xu, C.; Zhu, H. L.; Tan, R. X., Chaetominine, a cytotoxic alkaloid produced by endophytic Chaetomium sp. IFB-E015. *Org. Lett.* **2006,** *8* (25), 5709-5712.
[50] Zhang, L.; Li, Z.; Bai, J.; Wu, X.; Wang, Y.; Hua, H., Metabolites of Aspergillus sp. HT-2. *Zhongguo Yaoxue Zazhi (Beijing, China)* **2011,** *46* (15), 1154-1158.
[51] (a) Xu, C.-P.; Luo, S.-P.; Wang, A.-E.; Huang, P.-Q., Complexity generation by chemical synthesis: a five-step synthesis of (-)-chaetominine from l-tryptophan and its biosynthetic implications. *Org. Biomol. Chem.* **2014,** *12* (18), 2859-2863; (b) Deng, X.; Liang, K.; Tong, X.; Ding, M.; Li, D.; Xia, C., Biomimetic synthesis of (-)-chaetominine epimers via copper-catalyzed radical cyclization. *Tetrahedron* **2015,** *71* (22), 3699-3704.
[52] (a) Peng, Q.-L.; Luo, S.-P.; Xia, X.-E.; Liu, L.-X.; Huang, P.-Q., The four-step total synthesis of (-)-chaetominine. *Chem. Commun. (Cambridge, U. K.)* **2014,** *50* (16), 1986-1988; (b) Luo, S.-P.; Peng, Q.-L.; Xu, C.-P.; Wang, A.-E.; Huang, P.-Q., Bio-inspired Step-Economical, Redox-Economical and Protecting-Group-Free Enantioselective Total Syntheses of (-)-Chaetominine and Analogues. *Chin. J. Chem.* **2014,** *32* (8), 757-770.
[53] Lin, Z.-J.; Lu, Z.-Y.; Zhu, T.-J.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M., Penicillenols from Penicillium sp. GQ-7, an endophytic fungus associated with Aegiceras corniculatum. *Chem. Pharm. Bull.* **2008,** *56* (2), 217-221.
[54] Kempf, K.; Schmitt, F.; Bilitewski, U.; Schobert, R., Synthesis, stereochemical assignment, and bioactivity of the Penicillium metabolites penicillenols B1 and B2. *Tetrahedron* **2015,** *71* (31), 5064-5068.
[55] (a) Sengoku, T.; Wierzejska, J.; Takahashi, M.; Yoda, H., First stereoselective synthesis of penicillenol A1 via novel O- to C-acyl rearrangement of O-acyltetramic acid. *Synlett* **2010,** (19), 2944-2946; (b) Sengoku, T.; Nagae, Y.; Ujihara, Y.; Takahashi, M.; Yoda, H., A Synthetic Approach to Diverse 3-Acyltetramic Acids via O- to C-Acyl Rearrangement and Application to the Total Synthesis of Penicillenol Series. *J. Org. Chem.* **2012,** *77* (9), 4391-4401.
[56] Maloney, K. N.; Hao, W.; Xu, J.; Gibbons, J.; Hucul, J.; Roll, D.; Brady, S. F.; Schroeder, F. C.; Clardy, J., Phaeosphaeride A, an inhibitor of STAT3-dependent signaling isolated from an endophytic fungus. *Org. Lett.* **2006,** *8* (18), 4067-4070.
[57] Kobayashi, K.; Kobayashi, Y.; Nakamura, M.; Tamura, O.; Kogen, H., Establishment of Relative and Absolute Configurations of Phaeosphaeride A: Total Synthesis of ent-Phaeosphaeride A. *J. Org. Chem.* **2015,** *80* (2), 1243-1248.
[58] (a) Kobayashi, K.; Okamoto, I.; Morita, N.; Kiyotani, T.; Tamura, O., Synthesis of the proposed structure of phaeosphaeride A. *Org. Biomol. Chem.* **2011,** *9* (16), 5825-5832; (b) Chatzimpaloglou, A.; Yavropoulou, M. P.; Rooij, K. E.; Biedermann, R.; Mueller, U.; Kaskel, S.; Sarli, V., Total Synthesis and Biological Activity of the Proposed Structure of Phaeosphaeride A. *J. Org. Chem.* **2012,** *77* (21), 9659-9667; (c) Chatzimpaloglou, A.; Kolosov, M.; Eckols, T. K.; Tweardy, D. J.; Sarli, V., Synthetic and Biological Studies of Phaeosphaerides. *J. Org. Chem.* **2014,** *79* (9), 4043-4054.
[59] Tanasova, M.; Sturla, S. J., Chemistry and Biology of Acylfulvenes: Sesquiterpene-Derived Antitumor Agents. *Chem. Rev. (Washington, DC, U. S.)* **2012,** *112* (6), 3578-3610.
[60] Stevens-Cullinane, L.; Lucas, N. T.; Hawkins, B. C., Sterically controlled Diels-Alder cycloadditions. Rapid entry into the illudin scaffold. *Eur. J. Org. Chem.* **2014,** *2014* (22), 4767-4772.
[61] (a) Chokpaiboon, S.; Sommit, D.; Teerawatananond, T.; Muangsin, N.; Bunyapaiboonsri, T.; Pudhom, K., Cytotoxic Nor-chamigrane and Chamigrane Endoperoxides from a Basidiomycetous Fungus. *J. Nat. Prod.* **2010,** *73* (5), 1005-1007; (b) Li, H.; Huang, H.; Shao, C.; Huang, H.; Jiang, J.; Zhu, X.; Liu, Y.; Liu, L.; Lu, Y.; Li, M.; Lin, Y.; She, Z., Cytotoxic norsesquiterpene peroxides from the endophytic fungus Talaromyces flavus isolated from the mangrove plant Sonneratia apetala. *J. Nat. Prod.* **2011,** *74* (5), 1230-1235.
[62] Chen, H.-J.; Wu, Y., Expeditious Entry to the Chamigrane Endoperoxide Family of Natural Products. *Org. Lett.* **2015,** *17* (3), 592-595.

[63] Toyota, M.; Ihara, M., Total synthesis of aphidicolane and stemodane diterpenes. *Tetrahedron* **1999,** *55* (18), 5641-5679.
[64] Banerjee, A. K.; Laya, M. S.; Mora, H. R.; Cabrera, E. V., The chemistry of bioactive diterpenes. *Curr. Org. Chem.* **2008,** *12* (13), 1050-1070.
[65] Zhong, W.; Little, R. D., Intramolecular diyl trapping reactions en route to the bicyclo [3.2.1] framework; an approach to aphidicolin. *Tetrahedron Lett.* **2009,** *50* (35), 4994-4997.
[66] Mizushina, Y.; Iida, A.; Ohta, K.; Sugawara, F.; Sakaguchi, K., Novel triterpenoids inhibit both DNA polymerase and DNA topoisomerase. *Biochem. J.* **2000,** *350* (3), 757-763.
[67] Yamaoka, M.; Nakazaki, A.; Kobayashi, S., Total synthesis of fomitellic acid B. *Tetrahedron Lett.* **2009,** *50* (49), 6764-6768.
[68] (a) Wipf, P.; Halter, R. J., Chemistry and biology of wortmannin. *Org. Biomol. Chem.* **2005,** *3* (11), 2053-2061; (b) Jacobi, P. A.; Konekamp, T.; Mascall, K. C.; O'Connor, R. T.; Onyango, E. O.; Sessions, E. H., Constructing the heterocyclic core of viridin and wortmannin. *Adv. Heterocycl. Chem.* **2013,** *110*, 119-143.
[69] Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J., Torreyanic acid: a selectively cytotoxic quinone dimer from the endophytic fungus Pestalotiopsis microspora. *J. Org. Chem.* **1996,** *61* (10), 3232-3233.
[70] Li, C.; Lobkovsky, E.; Porco, J. A., Jr., Total Synthesis of (±)-Torreyanic Acid. *J. Am. Chem. Soc.* **2000,** *122* (42), 10484-10485.
[71] Li, C.; Johnson, R. P.; Porco, J. A., Jr., Total Synthesis of the Quinone Epoxide Dimer (+)-Torreyanic Acid: Application of a Biomimetic Oxidation/Electrocyclization/Diels-Alder Dimerization Cascade. *J. Am. Chem. Soc.* **2003,** *125* (17), 5095-5106.
[72] Mehta, G.; Pan, S. C., Total Synthesis of the Novel, Biologically Active Epoxyquinone Dimer (±)-Torreyanic Acid: A Biomimetic Approach. *Org. Lett.* **2004,** *6* (22), 3985-3988.
[73] Wijeratne, E. M. K.; Paranagama, P. A.; Marron, M. T.; Gunatilaka, M. K.; Arnold, A. E.; Gunatilaka, A. A. L., Sesquiterpene quinones and related metabolites from Phyllosticta spinarum, a fungal strain endophytic in Platycladus orientalis of the Sonoran desert. *J. Nat. Prod.* **2008,** *71* (2), 218-222.
[74] Ishii, S.; Fujii, M.; Akita, H., First syntheses of (-)-tauranin and antibiotic (-)-BE-40644 based on lipase-catalyzed optical resolution of albicanol. *Chem. Pharm. Bull.* **2009,** *57* (10), 1103-1106.
[75] (a) Balan, J.; Fuska, J.; Kuhr, I.; Kuhrova, V., Bikaverin, an antibiotic from Gibberella fujikuroi, effective against Leishmania brasiliensis. *Folia Microbiol. (Prague)* **1970,** *15* (6), 479-484; (b) Zhan, J.; Burns, A. M.; Liu, M. X.; Faeth, S. H.; Gunatilaka, A. A. L., Search for cell motility and angiogenesis inhibitors with potential anticancer activity: Beauvericin and other constituents of two endophytic strains of Fusarium oxysporum. *J. Nat. Prod.* **2007,** *70* (2), 227-232.
[76] Bekaert, A.; Andrieux, J.; Plat, M., New total synthesis of bikaverin. *Tetrahedron Lett.* **1992,** *33* (20), 2805-2806.
[77] Deshpande, V. H.; Khan, R. A.; Ayyangar, N. R., Regiospecific synthesis of bikaverin. *Synth. Commun.* **1993,** *23* (19), 2677-2682.
[78] Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M., Regiospecific preparation of the benz[b]xanthen-12-one ring system. Total synthesis of bikaverin. *J. Org. Chem.* **1988,** *53* (1), 223-224.
[79] De Koning, C. B.; Giles, R. G. F.; Engelhardt, L. M.; White, A. H., Convenient syntheses of the naturally occurring benzo[b]xanthen-12-one bikaverin. X-ray crystallographic confirmation of the product regiochemistry. *J. Chem. Soc., Perkin Trans. 1* **1988,** (12), 3209-3216.
[80] Barton, D. H. R.; Cottier, L.; Freund, K.; Luini, F.; Magnus, P. D.; Salaza, I., Total synthesis of bikaverin (6,11-dihydroxy-3,8-dimethoxy-1-methyl-benzo[b]xanthene-7,10,12-trione). *J. Chem. Soc., Perkin Trans. 1* **1976,** (5), 499-503.
[81] Katagiri, N.; Nakano, J.; Kato, T., Synthesis of bikaverin. *J. Chem. Soc., Perkin Trans. 1* **1981,** (10), 2710-2716.
[82] Song, Y. C.; Li, H.; Ye, Y. H.; Shan, C. Y.; Yang, Y. M.; Tan, R. X., Endophytic naphthopyrone metabolites are co-inhibitors of xanthine oxidase, SW1116 cell and some microbial growths. *FEMS Microbiol. Lett.* **2004,** *241* (1), 67-72.
[83] (a) Shibata, S.; Morishita, E.; Arima, Y., Synthesis of rubrofusarin dimethyl ether. *Chem. Pharm. Bull.* **1963,** *11*, 821-823; (b) Shibata, S.; Morishita, E.; Arima, Y., Metabolic products of fungi. XXV. Synthesis of rubrofusarin and its derivatives. *Chem. Pharm. Bull. (Tokyo)* **1967,** *15* (11), 1757-1764.
[84] Leeper, F. J.; Staunton, J., Biomimetic syntheses of polyketide aromatics from reaction of an orsellinate anion with pyrones and a pyrylium salt. *J. Chem. Soc., Perkin Trans. 1* **1984,** (5), 1053-1059.
[85] Alvi, K. A.; Rodriguez, J.; Diaz, M. C.; Moretti, R.; Wilhelm, R. S.; Lee, R. H.; Slate, D. L.; Crews, P., Protein tyrosine kinase inhibitory properties of planar polycyclics obtained from the marine sponge Xestospongia cf. carbonaria and from total synthesis. *J. Org. Chem.* **1993,** *58* (18), 4871-4880.
[86] Harada, N.; Sugioka, T.; Ando, Y.; Uda, H.; Kuriki, T., Total synthesis of (+)-halenaquinol and (+)-halenaquinone. Experimental proof of their absolute stereostructures theoretically determined. *J. Am. Chem. Soc.* **1988,** *110* (25), 8483-8487.

[87] (a) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M., Catalytic Asymmetric Synthesis of Halenaquinone and Halenaquinol. *J. Org. Chem.* **1996,** *61* (15), 4876-4877; (b) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M., Catalytic asymmetric synthesis of halenaquinone and halenaquinol. *Synthesis* **1998,** (Spec.), 581-589; (c) Shibasaki, M.; Kojima, A.; Shimizu, S., Catalytic asymmetric synthesis of natural products with heterocyclic rings. *J. Heterocycl. Chem.* **1998,** *35* (5), 1057-1064.
[88] (a) Toyooka, N.; Nagaoka, M.; Kakuda, H.; Nemoto, H., Rapid access to the potential intermediate for the synthesis of halenaquinol and halenaquinone. *Synlett* **2001,** (7), 1123-1124; (b) Toyooka, N.; Nagaoka, M.; Sasaki, E.; Qin, H.; Kakuda, H.; Nemoto, H., Model studies toward the total synthesis of halenaquinol and halenaquinone. *Tetrahedron* **2002,** *58* (30), 6097-6101.
[89] Sutherland, H. S.; Souza, F. E. S.; Rodrigo, R. G. A., A Short Synthesis of (±)-Halenaquinone. *J. Org. Chem.* **2001,** *66* (10), 3639-3641.
[90] Kienzler, M. A.; Suseno, S.; Trauner, D., Vinyl Quinones as Diels-Alder Dienes: Concise Synthesis of (-)-Halenaquinone. *J. Am. Chem. Soc.* **2008,** *130* (27), 8604-8605.
[91] (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J., Cytoskyrins A and B, new BIA active bisanthraquinones isolated from an endophytic fungus. *Org. Lett.* **2000,** *2* (25), 4047-4049; (b) Singh, M. P.; Janso, J. E.; Brady, S. F., Cytoskyrins and cytosporones produced by Cytospora sp. CR200: taxonomy, fermentation and biological activities. *Mar. Drugs* **2007,** *5* (3), 71-84.
[92] Takeda, N.; Seo, S.; Ogihara, Y.; Sankawa, U.; Iitaka, I.; Kitagawa, I.; Shibata, S., Fungal metabolites. XXXI. Anthraquinonoid coloring matters of penicillium islandicum and other fungi. (-)-Luteoskyrin, (-)-rubroskyrin, (+)-rugulosin and their related compounds. *Tetrahedron* **1973,** *29* (22), 3703-3719.
[93] (a) Nicolaou, K. C.; Chen, J. S., Total synthesis of complex heterocyclic natural products. *Pure Appl. Chem.* **2008,** *80* (4), 727-742; (b) Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D., Total Syntheses of 2,2'-epi-Cytoskyrin A, Rugulosin, and the Alleged Structure of Rugulin. *J. Am. Chem. Soc.* **2007,** *129* (13), 4001-4013; (c) Nicolaou, K. C.; Papageorgiou, C. D.; Piper, J. L.; Chadha, R. K., The cytoskyrin cascade: A facile entry into cytoskyrin A, deoxyrubroskyrin, rugulin, skyrin, and flavoskyrin model systems. *Angew. Chem., Int. Ed.* **2005,** *44* (36), 5846-5851; (d) Nicolaou, K. C.; Lim, Y. H.; Papageorgiou, C. D.; Piper, J. L., Total synthesis of (+)-rugulosin and (+)-2,2'-epi-cytoskyrin A through cascade reactions. *Angew. Chem., Int. Ed.* **2005,** *44* (48), 7917-7921.
[94] Xia, X.; Li, Q.; Li, J.; Shao, C.; Zhang, J.; Zhang, Y.; Liu, X.; Lin, Y.; Liu, C.; She, Z., Two new derivatives of griseofulvin from the mangrove endophytic fungus Nigrospora sp. (strain No. 1403) from Kandelia candel (L.) druce. *Planta Med.* **2011,** *77* (15), 1735-1738.
[95] Larsen, D. S.; Stoodley, R. J., An enantioselective synthesis of (+)-bostrycin leading to a revision of the absolute configuration of its natural antipode. *Tetrahedron* **1990,** *46* (13-14), 4711-4732.
[96] Chen, H.; Zhong, L.; Long, Y.; Li, J.; Wu, J.; Liu, L.; Chen, S.; Lin, Y.; Li, M.; Zhu, X.; She, Z., Studies on the synthesis of derivatives of marine-derived bostrycin and their structure-activity relationship against tumor cells. *Mar. Drugs* **2012,** *10*, 932-952.
[97] Suemitsu, R.; Matsui, Y.; Hiura, M., Metabolic products of Macrosporium porri. I. Isolation and general properties of macrosporin, a new pigment. *Bull. Agric. Chem. Soc. Jpn.* **1957,** *21*, 1-4.
[98] Aly, A. H.; Edrada-Ebel, R.; Wray, V.; Mueller, W. E. G.; Kozytska, S.; Hentschel, U.; Proksch, P.; Ebel, R., Bioactive metabolites from the endophytic fungus Ampelomyces sp. isolated from the medicinal plant Urospermum picroides. *Phytochemistry (Elsevier)* **2008,** *69* (8), 1716-1725.
[99] Brisson, C.; Brassard, P., Regiospecific reactions of some vinylogous ketene acetals with haloquinones and their regioselective formation by dienolization. *J. Org. Chem.* **1981,** *46* (9), 1810-1814.
[100] Cordes, J.; Barrett, A. G. M., Synthesis of macrosporin and related 9,10-anthraquinones by biomimetic polyketide aromatization and cyclization of 6-benzylresorcylates. *Eur. J. Org. Chem.* **2013,** *2013* (7), 1318-1326.
[101] Khan, A. T.; Blessing, B.; Schmidt, R. R., An expedient and efficient synthesis of naturally occurring hydroxy-substituted anthraquinones. *Synthesis* **1994,** (3), 255-257.
[102] Castonguay, A.; Brassard, P., C-Alkylation of 1,3-dihydroxyanthraquinones. Total synthesis of (±)-averufin and (±)-bipolarin. *Can. J. Chem.* **1977,** *55* (8), 1324-1332.
[103] O'Malley, G. J.; Murphy, R. A., Jr.; Cava, M. P., Aflatoxin precursors: total synthesis of (±)-averufin and (±)-nidurufin. *J. Org. Chem.* **1985,** *50* (26), 5533-5537.
[104] Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P., Methoxymethyl-directed aryl metalation. Total synthesis of (±)-averufin. *J. Am. Chem. Soc.* **1981,** *103* (23), 6885-6888.
[105] Tan, H.; Chen, X.; Chen, H.; Liu, H.; Qiu, S., Proline-Catalyzed Knoevenagel Condensation/[4+2] Cycloaddition Cascade Reaction: Application to Formal Synthesis of Averufin. *Eur. J. Org. Chem.* **2015,** *2015* (22), 4956-4963.
[106] (a) Conradt, D.; Schaetzle, M. A.; Haas, J.; Townsend, C. A.; Mueller, M., New Insights into the Conversion of Versicolorin A in the Biosynthesis of Aflatoxin B1. *J. Am. Chem. Soc.* **2015,** *137* (34), 10867-10869; (b) Graybill, T. L.; Casillas, E. G.; Pal, K.; Townsend, C. A., Silyl Triflate-Mediated Ring-Closure and Rearrangement in the Synthesis of Potential Bisfuran-Containing Intermediates of Aflatoxin Biosynthesis. *J. Am. Chem. Soc.* **1999,** *121* (34), 7729-7746; (c) Graybill, T. L.; Pal, K.; McGuire, S. M.; Brobst, S. W.; Townsend, C. A., The timing of aromatic deoxygenation in aflatoxin biosynthesis. *J. Am. Chem. Soc.* **1989,** *111* (21), 8306-8.

[107] (a) Ishiyama, D.; Kanai, Y.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Kanazawa, S., Novel human topoisomerase I inhibitors, topopyrones A, B, C and D. II. Structure elucidation. *J. Antibiot.* **2000,** *53* (9), 873-878; (b) Kanai, Y.; Ishiyama, D.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Tokumasu, S.; Kanazawa, S., Novel human topoisomerase I inhibitors, topopyrones A, B, C and D. I. Producing strain, fermentation, isolation, physico-chemical properties and biological activity. *J. Antibiot.* **2000,** *53* (9), 863-872.
[108] (a) Tan, J. S.; Ciufolini, M. A., Total Synthesis of Topopyrones B and D. *Org. Lett.* **2006,** *8* (21), 4771-4774; (b) Turner, C. D.; Ciufolini, M. A., Directed aromatic functionalization in natural-product synthesis: fredericamycin A, nothapodytine B, and topopyrones B and D. *Beilstein J. Org. Chem.* **2011,** *7*, 1475-1485, No. 171.
[109] (a) Gattinoni, S.; Merlini, L.; Dallavalle, S., First total synthesis of Topopyrone C. *Tetrahedron Lett.* **2007,** *48* (6), 1049-1051; (b) Dallavalle, S.; Gattinoni, S.; Mazzini, S.; Scaglioni, L.; Merlini, L.; Tinelli, S.; Beretta, G. L.; Zunino, F., Synthesis and cytotoxic activity of a new series of topoisomerase I inhibitors. *Bioorg. Med. Chem. Lett.* **2008,** *18* (4), 1484-1489.
[110] (a) Elban, M. A.; Hecht, S. M., Total Synthesis of the Topopyrones: A New Class of Topoisomerase I Poisons. *J. Org. Chem.* **2008,** *73* (3), 785-793; (b) Zaleski, P. A.; Maini, R.; Leiris, S. J.; Elban, M. A.; Hecht, S. M., Synthesis and Biological Activities of Topopyrones. *J. Nat. Prod.* **2012,** *75* (4), 577-585.
[111] Font, A. M., Pigments of spurred rye. *Ann. Physiol. Veg.* **1968,** *10* (4), 277-298.
[112] Yu, M.-l.; Xu, B.; Cheng, F.; Zou, K.; Chen, J.-f., The study of antitumor secondary metabolites from Penicillium oxalicum, a fungus residing in Acrida cinerea. *Tianran Chanwu Yanjiu Yu Kaifa* **2014,** *26* (8), 1165-1169.
[113] Qin, T.; Porco, J. A., Jr., Total Syntheses of Secalonic Acids A and D. *Angew. Chem., Int. Ed.* **2014,** *53* (12), 3107-3110.
[114] Qin, T.; Johnson, R. P.; Porco, J. A., Jr., Vinylogous Addition of Siloxyfurans to Benzopyryliums: A Concise Approach to the Tetrahydroxanthone Natural Products. *J. Am. Chem. Soc.* **2011,** *133* (6), 1714-1717.
[115] Wezeman, T.; Masters, K.-S.; Brase, S., Double trouble--the art of synthesis of chiral dimeric natural products. *Angew Chem Int Ed Engl* **2014,** *53* (18), 4524-4526.
[116] Ganapathy, D.; Reiner, J. R.; Loeffler, L. E.; Ma, L.; Gnanaprakasam, B.; Niepoetter, B.; Koehne, I.; Tietze, L. F., Enantioselective Total Synthesis of Secalonic Acid E. *Chem. - Eur. J.* **2015,** *21* (47), 16807-16810.
[117] Qin, T.; Iwata, T.; Ransom, T. T.; Beutler, J. A.; Porco, J. A., Syntheses of Dimeric Tetrahydroxanthones with Varied Linkages: Investigation of "Shapeshifting" Properties. *J. Am. Chem. Soc.* **2015,** *137* (48), 15225-15233.
[118] Schmidt, B.; Riemer, M.; Schilde, U., Tandem Claisen Rearrangement/6-endo Cyclization Approach to Allylated and Prenylated Chromones. *Eur. J. Org. Chem.* **2015,** *2015* (34), 7602-7611.
[119] N. Sciaky, J. P., C. Smith, K. J.M. Zaal, N. Cole, J. E. Moreira, M. Terasaki, E. Siggia, J. Lippincott-Schwartz, Golgi tubule traffic and the effects of brefeldin A visualized in living cells. *J. Cell. Biol.* **1997,** *139*, 1137-1155.
[120] Koch, K.; Podlech, J.; Pfeiffer, E.; Metzler, M., Total synthesis of alternariol. *J Org Chem* **2005,** *70* (8), 3275-3276.
[121] (a) Won, M.; Kwon, S.; Kim, T.-H., An efficient synthesis of Alternariol. *J. Korean Chem. Soc.* **2015,** *59* (5), 471-474; (b) Abe, H.; Fukumoto, T.; Takeuchi, Y.; Harayama, T., Synthesis of alternariol through an intramolecular biaryl coupling reaction using palladium reagent. *Heterocycles* **2007,** *74*, 265-271.
[122] Singleton, V. L. B., N.; Ullstrupp, A. J. , Decumbin, a new compound from a species of Penicillium. *Nature* **1958,** *181*, 1072-1073.
[123] Corey, E. J. W., R. H. , Total Synthesis of Brefeldin A. *Tetrahedron Lett.* **1976**, 4705-4708.
[124] Wu, Y.; Gao, J., Total Synthesis of (+)-Brefeldin A. *Org. Lett.* **2008,** *10* (8), 1533-1536.
[125] Archambaud, S.; Legrand, F.; Aphecetche-Julienne, K.; Collet, S.; Guingant, A.; Evain, M., Total Synthesis of (+)-Brefeldin C, (+)-nor-Me Brefeldin A and (+)-4-epi-nor-Me Brefeldin A. *Eur. J. Org. Chem.* **2010,** (7), 1364-1380, S1364/1-S1364/49.
[126] Inai, M.; Nishii, T.; Mukoujima, S.; Esumi, T.; Kaku, H.; Tominaga, K.; Abe, H.; Horikawa, M.; Tsunoda, T., Total synthesis of (+)-brefeldin C utilizing aza-Claisen rearrangement. *Synlett* **2011,** (10), 1459-1461.
[127] Yadav, J. S.; Sreedhar, P.; Srihari, P.; Sarma, G. D.; Jagadeesh, B., The concise synthesis of a key intermediate for the total synthesis of fumagillin, TNP-470, and ovalicin. *Synthesis* **2008,** (9), 1460-1466.
[128] Fuchs, M.; Fuerstner, A., trans-Hydrogenation: Application to a Concise and Scalable Synthesis of Brefeldin A. *Angew. Chem., Int. Ed.* **2015,** *54* (13), 3978-3982.
[129] C. M. Daddario, Q. H., M. Zeller and G. Sauve, *European Journal of Inorganic Chemistry* **2015**, 3649-3657.
[130] (a) H.-W. Zhang, W.-Y. H., Y.-C. Song, J.-R. Chen, R.-X. Tan, Four 6H-Dibenzo [b, d] pyran-6-one Derivatives Produced by the Endophyte Cephalosporium acremonium IFB-E007. *Helv. Chim. Acta* **2005,** *88*, 2861-2864; (b) Altemoeller, M.; Gehring, T.; Cudaj, J.; Podlech, J.; Goesmann, H.; Feldmann, C.; Rothenberger, A., Total synthesis of graphislactones A, C, D, and H, of ulocladol, and of the originally proposed and revised structures of graphislactones E and F. *Eur. J. Org. Chem.* **2009,** (13), 2130-2140, and references cited herein.
[131] Cudaj, J.; Podlech, J., Total synthesis of graphislactone G. *Tetrahedron Lett.* **2010,** *51* (23), 3092-3094.
[132] M. Chu, R. M., L. Xu, L. He, J. Terracciano, M. Patel, V. Gullo, T. Black, W. Zhao, T. Chan and A. T. McPhail, Isolation and Structure Elucidation of Sch 642305, a Novel Bacterial DNA Primase Inhibitor Produced by Penicillium verrucosum. *J. Nat. Prod.* **2003,** *66*, 1527-1530.

[133] H. Jayasuriya, D. L. Z., J. D. Polishook, G. F. Bills, A. W. Dombrowski, O. Genilloud, F. F. Pelacz, L. Herranz, D. Quamina, R. B. Lingham, R. Danzeizem, P. L. Graham, J. E. Tomassini and S. B. Singh, Chem. Biodiversity, 2005, 2, 112., Identification of Diverse Microbial Metabolites as Potent Inhibitors of HIV-1 Tat Transactivation. *Chem. Biodiversity* **2005,** *2*, 112-122.
[134] Mehta, G.; Shinde, H. M., Enantioselective total synthesis of bioactive natural product (+)-Sch 642305: a structurally novel inhibitor of bacterial DNA primase and HIV-1 Tat transactivation. *Chem. Commun. (Cambridge, U. K.)* **2005,** (29), 3703-3705.
[135] Ishigami, K.; Katsuta, R.; Watanabe, H., Stereoselective synthesis of Sch 642305, an inhibitor of bacterial DNA primase. *Tetrahedron* **2006,** *62* (10), 2224-2230.
[136] Snider, B. B.; Zhou, J., Synthesis of (+)-Sch 642305 by a Biomimetic Transannular Michael Reaction. *Org. Lett.* **2006,** *8* (7), 1283-1286.
[137] Fujioka, H.; Ohba, Y.; Nakahara, K.; Takatsuji, M.; Murai, K.; Ito, M.; Kita, Y., New Perspective for Natural Products Synthesis: Concise Synthesis of (+)-Sch 642305 by Chiral Auxiliary Multiuse Methodology. *Org. Lett.* **2007,** *9* (26), 5605-5608.
[138] Wilson, E. M.; Trauner, D., Concise synthesis of the bacterial DNA primase inhibitor (+) -Sch 642305. *Org Lett* **2007,** *9* (7), 1327-1329.
[139] Arnone, A. C., R.; Meille, S. V.; Nasini, G.; Tollazi, M. , *J. Chem. Soc., Perkin Trans. 1* **1994**, 2165−2168.
[140] Merlini, L. N., G.; Scaglioni, L.; Cassinelli, G.; Lanzi, C. Phytochem- istry 2000, 53, 1039., Structure elucidation of clavilactone D: an inhibitor of protein tyrosine kinases. *Phytochemistry 2000* **2000,** *53*, 1039-1041.
[141] Cassinelli, G. L., C.; Pensa, T.; Gambetta, R. A.; Nasini, G.; Cuccuru, G.; Cassinis, M.; Pratesi, G.; Polizzi, D.; Tortoreto, M.; Zunino, F. , Clavilactones, a novel class of tyrosine kinase inhibitors of fungal origin. *Biochem. Pharmacol. 1539−1547.* **2000,** *59*, 1539-1547.
[142] Larrosa, I.; Da, S. M. I.; Gomez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M., Highly convergent three component benzyne coupling: the total synthesis of ent-clavilactone B. *J Am Chem Soc* **2006,** *128* (43), 14042-14043.
[143] (a) Takao, K.-i.; Nanamiya, R.; Fukushima, Y.; Namba, A.; Yoshida, K.; Tadano, K.-i., Total Synthesis of (+)-Clavilactone A and (-)-Clavilactone B by Ring-Opening/Ring-Closing Metathesis. *Org. Lett.* **2013,** *15* (21), 5582-5585; (b) Takao, K.-i.; Yoshida, K.; Tadano, K.-i., Total synthesis of natural products using sequential olefin metathesis reactions. *Yuki Gosei Kagaku Kyokaishi* **2015,** *73* (12), 1192-1199.
[144] Lv, L.; Shen, B.; Li, Z., Total synthesis of (±)-clavilactones A, B, and proposed D through iron-catalyzed carbonylation-peroxidation of olefin. *Angew. Chem., Int. Ed.* **2014,** *53* (16), 4164-4167.
[145] Suizu, H.; Shigeoka, D.; Aoyama, H.; Yoshimitsu, T., Total synthesis of clavilactone B: a radical cyclization-fragmentation strategy. *Org Lett* **2015,** *17* (1), 126-129.
[146] Cooper, J. A., Effects of Cytochalasin and Phalloidin on Actin. *J. Cell. Biol.* **1987,** *105*, 1473-1478.
[147] Scherlach, K.; Boettger, D.; Remme, N.; Hertweck, C., The chemistry and biology of cytochalasans. *Nat. Prod. Rep.* **2010,** *27*, 869-886.
[148] Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J., Total synthesis of cytochalasin B. *J. Am. Chem. Soc.* **1978,** *100* (24), 7775-7777.
[149] Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J., Palladium-catalyzed synthesis of macrocycles. A total synthesis of (-)-aspochalasin B. *J. Am. Chem. Soc.* **1989,** *111* (21), 8281-4.
[150] Haidle, A. M.; Myers, A. G., An Enantioselective, Modular, and General Route to the Cytochalasins: Synthesis of L-696,474 and Cytochalasin B. *PNAS* **2004,** *101* (33), 12048-12053.
[151] Zhou, J.-H.; Cai, S.-H.; Xu, Y.-H.; Loh, T.-P., Anomalous Reactivity and Selectivity in the Intermolecular Diels-Alder Reactions of Multisubstituted Acyclic Dienes with Geometrical Isomers of Enals. *Org. Lett.* **2016,** *18* (10), 2355-2358.
[152] A. Numata, T. A., K. Minoura, T. Ito, Gymnastatins, novel cytotoxic metabolites produced by a fungal strain from a sponge. *Tetrahedron Lett.* **1997,** *38*, 5675-5678.
[153] Hayakawa, Y., Structure–activity relationship analysis,. *Cancer Chemother* **2004,** *31*, 526-528.
[154] Gurjar, M. K.; Bhaket, P., Total synthesis of a novel cytotoxic metabolite gymnastatin A. *Heterocycles* **2000,** *53* (1), 143-149.
[155] Amagata, T.; Minoura, K.; Numata, A., Structures for cytotoxic metabolites of a fungus separated from a sponge and total synthesis of gymnastatin I. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1998,** *40th*, 115-120.
[156] Phoon, C. W.; Somanadhan, B.; Heng, S. C. H.; Ngo, A.; Ng, S. B.; Butler, M. S.; Buss, A. D.; Sim, M. M., Isolation and total synthesis of gymnastatin N, a POLO-like kinase 1 active constituent from the fungus Arachniotus punctatus. *Tetrahedron* **2004,** *60* (50), 11619-11628.
[157] Ogamino, T.; Ohnishi, S.; Ishikawa, Y.; Sugai, T.; Obata, R.; Nishiyama, S., Synthesis and biological assessment of hemiacetal spiro derivatives towards development of efficient chemotherapeutic agent. *Sci. Technol. Adv. Mater.* **2006,** *7* (2), 175-183.
[158] Raffier, L.; Piva, O., Application of the diastereoselective photodeconjugation of α,β-unsaturated esters to the synthesis of gymnastatin H. *Beilstein J. Org. Chem.* **2011,** *7*, 151-155, No. 21.
[159] Kakeya, H. T., I.; Okada, G.; Isono, K.; Osada, H. , Epolactaene, a Novel Neuritogenic Compound

in HumanNeuroblastoma Cells, Produced by a Marine Fungus. *J. Antibiot.* **1995,** *48*, 733-735.
[160] Kakeya, H. O., C.; Sato, M.; Arai, K.; Osada, Neuritogenic Effect of Epolactaene Derivatives on Human Neuroblastoma Cells Which Lack High-Affinity Nerve Growth Factor Receptors. *J. Med. Chem.* **1997,** *40*, 391-394.
[161] (a) Marumoto, S.; Kogen, H.; Naruto, S., Absolute Configuration and Total Synthesis of (+)-Epolactaene, a Neuritogenic Agent from Penicillium sp. BM 1689-P Active in Human Neuroblastoma Cells. *J. Org. Chem.* **1998,** *63* (7), 2068-2069; (b) Kuramochi, K.; Nagata, S.; Itaya, H.; Takao, K.-I.; Kobayashi, S., Convergent total synthesis of epolactaene: application of bridgehead oxiranyl anion strategy. *Tetrahedron Lett.* **1999,** *40* (41), 7371-7374; (c) Marumoto, S.; Kogen, H.; Naruto, S., Asymmetric total synthesis of epolactaene. Part 2: introduction of the side chain and synthesis of (+)-epolactaene and its enantiomer. *Tetrahedron* **1999,** *55* (23), 7145-7156; (d) Marumoto, S.; Kogen, H., Asymmetric total synthesis of epolactaene. *Yuki Gosei Kagaku Kyokaishi* **2000,** *58* (3), 183-191.
[162] Kuramochi, K.; Nagata, S.; Itaya, H.; Matsubara, Y.; Sunoki, T.; Uchiro, H.; Takao, K.-i.; Kobayashi, S., A convergent total synthesis of epolactaene: an application of the bridgehead oxiranyl anion strategy. *Tetrahedron* **2003,** *59* (49), 9743-9758.
[163] Tan, Z.; Negishi, E.-I., Selective Synthesis of Epolactaene Featuring Efficient Construction of Methyl (Z)-2-Iodo-2-butenoate and (2R,3S,4S)-2-Trimethylsilyl-2,3-epoxy-4-methyl-γ-butyrolactone. *Org. Lett.* **2006,** *8* (13), 2783-2785.
[164] Tajima, K.; Umehara, Y.; Kobayashi, K.; Kogen, H., Studies toward the second-generation synthesis of epolactaene: highly stereoselective construction of the epoxy-γ-lactam moiety. *Synlett* **2014,** *25* (16), 2337-2340.
[165] J. H. Killough, G. B. M., and R. C. Smith, The treatment of amebiasis with fumagillin. *Science* **1952,** *115*, 71-72.
[166] J. A. DiPaolo, D. S. T., and G. E. Moore,, *Antibiot. Annu.* **1958**, 541.
[167] Ingber, D. F., T.; Kishimoto, S.; Sudo, K.; Kanamaru, T.; Brem, H.; Folkman, J. , Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumour growth. *Nature* **1990,** *348*, 555-557.
[168] (a) Furness, M. S.; Robinson, T. P.; Ehlers, T.; Hubbard, R. B. I.; Arbiser, J. L.; Goldsmith, D. J.; Bowen, J. P., Antiangiogenic agents: studies on fumagillin and curcumin analogs. *Curr. Pharm. Des.* **2005,** *11* (3), 357-373; (b) Lefkove, B.; Govindarajan, B.; Arbiser, J. L., Fumagillin: an anti-infective as a parent molecule for novel angiogenesis inhibitors. *Expert Rev. Anti-Infect. Ther.* **2007,** *5* (4), 573-579.
[169] (a) Picoul, W.; Bedel, O.; Haudrechy, A.; Langlois, Y., Progress in fumagillin synthesis. *Pure Appl. Chem.* **2003,** *75* (2-3), 235-249; (b) Bedel, O.; Haudrechy, A.; Pouilhes, A.; Langlois, Y., Syntheses of antiangiogenic or cytotoxic natural products: fumagillin and bengacarboline. *Pure Appl. Chem.* **2005,** *77* (7), 1139-1152; (c) Yamaguchi, J.; Hayashi, Y., Syntheses of Fumagillin and Ovalicin. *Chem. - Eur. J.* **2010,** *16* (13), 3884-3901; (d) Gamba-Sanchez, D., Fumagillin and structurally related molecules as source of new drugs. *Mini-Rev. Org. Chem.* **2012,** *9* (2), 126-142.
[170] (a) Corey, E. J.; Snider, B. B., A total synthesis of ( )-fumagillin. *J Am Chem Soc* **1972,** *94* (7), 2549-2550; (b) D. A. Vosburg, S. W., E. J. Sorensen, A concise synthesis of fumagillol. *Angew. Chem. Ed.* **1999,** *38*; (c) M. Hutchings, D. M., N. S. Simpkins, A concise synthesis of fumagillol. *Synlett* **2001**, 661-663.
[171] Vosburg, D. A.; Weiler, S.; Sorensen, E. J., Concise stereocontrolled routes to fumagillol, fumagillin, and TNP-470. *Chirality* **2003,** *15* (2), 156-166.
[172] Yamaguchi, J.; Toyoshima, M.; Shoji, M.; Kakeya, H.; Osada, H.; Hayashi, Y., Concise enantio- and diastereoselective total syntheses of fumagillol, RK-805, FR65814, ovalicin, and 5-demethylovalicin. *Angew. Chem., Int. Ed.* **2006,** *45* (5), 789-793.
[173] Nagasawa, H. S., A.; Tamura, Isolation and structure of (+)-desoxyepiepoxydon and (+)-epiepoxydon, phytotoxic fungal metabolites. *Agric. Biol. Chem.* **1978,** *42*, 1303-1304.
[174] (a) Higa, T. O., R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. , Unprecedent constituents of a new specie of acorn worm. *Tetrahedron* **1987,** *43*, 1063-1070; (b) C. Klemke, S. K., A. D. Wright, G. M. Koenig, New Secondary Metabolites from the Marine Endophytic Fungus Apiospora m ontagnei. *J. Nat. Prod.* **2004,** *67*, 1058-1063; (c) H. Hussain, N. R., F. Jabeen, A. Al-Harrasi, A. Al-Rawahi, M. Ahmad, Z. Hassan, G. Abbas, F. Mabood, A. Shah, A. Badshah, A. Khan, R. Ahmad, I. R. Green, S. Draeger, B. Schulz, K. Krohn, Seimatoric acid and colletonoic acid: Two new compounds from the endophytic fungi, Seimatosporium sp. and Colletotrichum sp. *Chin. Chem. Lett.* **2014**, 1577-1579.
[175] (a) Kamikubo, T.; Hiroya, K.; Ogasawara, K., Stereo- and enantio-controlled synthesis of two naturally occurring polyoxygenated cyclohexenemethanols, (+)-epiepoxydon and (-)-phyllostine, via catalytic asymmetrization of a meso substrate. *Tetrahedron Lett.* **1996,** *37* (4), 499-502; (b) Tachihara, T.; Kitahara, T., Total synthesis of (+)-epiepoformin, (+)-epiepoxydon and (+)-bromoxone employing a useful chiral building block, ethyl (1R,2S)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate. *Tetrahedron* **2003,** *59* (10), 1773-1780.
[176] Mehta, G.; Islam, K., Enantioselective total synthesis of epoxyquinone natural products (-)-phyllostine, (+)-epoxydon, (+)-epiepoxydon and (-)-panepophenanthrin: access to versatile chiral building blocks through enzymatic kinetic resolution. *Tetrahedron Lett.* **2004,** *45* (41), 7683-7687.
[177] Fresneda, M. A.; Alibes, R.; Bayon, P.; Figueredo, M., Filling Some Blanks in a Divergent Approach to Gabosines: Enantioselective Synthesis of (-)-Epiepoxydon, (+)-Phyllostine, (-)-Gabosine D, and (-)-Gabosine E. *Eur. J. Org. Chem.* **2016,** *2016* (21), 3568-3574.

[178] Mehta, G.; Islam, K., Enantioselective total synthesis of (-)-epoxyquinols A and B. Novel, convenient access to chiral epoxyquinone building blocks through enzymatic desymmetrization. *Tetrahedron Lett.* **2004,** *45* (18), 3611-3615.
[179] Li, C.; Porco, J. A., Jr., Synthesis of epoxyquinol A and related molecules: probing chemical reactivity of epoxyquinol dimers and 2H-pyran precursors. *J Org Chem* **2005,** *70* (15), 6053-65.
[180] (a) Commeiras, L.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E.; Cowley, A. R.; Baker, C. M.; Albrecht, B.; Grant, G. H., Total synthesis of the epoxyquinol dimer (+)-panepophenanthrin: application of a diastereospecific biomimetic Diels-Alder dimerization. *Tetrahedron* **2006,** *62* (42), 9892-9901; (b) Shoji, M.; Hayashi, Y., Total synthesis of epoxyquinols: oxidative dimerization and its theoretical analysis. *Yuki Gosei Kagaku Kyokaishi* **2009,** *67* (2), 102-113.
[181] Gehrt, A. E., G.; Anke, H.; Anke, T.; Sterner, O., New Hexaketide Inhibitors of Eukaryotic Signal Transduction. *Nat. Prod. Lett.* **1997,** *9*, 259-264.
[182] Gehrt, A. E., G.; Anke, T.; Sterner, O. , Cycloepoxydon, 1-Hydroxy-2-hydroxymethyl-3-pent-1-enylbenzene and 1-Hydroxy-2-hydroxymethyl-3-pent-1, 3-dienylbenzene, New Inhibitors of Eukaryotic Signal Transduction. *J. Antibiot.* **1998,** *51*, 455-463.
[183] Mehta, G.; Islam, K., Total synthesis of the novel NF-kappaB inhibitor (-)-cycloepoxydon. *Org Lett* **2004,** *6* (5), 807-810.
[184] Erkel, G. A., T.; Sterner, O., Inhibition of NF-kappa B activation by panepoxydone. *Biochem. Biophys. Res. Commun.* **1996,** *226*, 214-221.
[185] Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L., Efficient stereoselective syntheses of isopanepoxydone and panepoxydone: a re-assignment of relative configuration. *Tetrahedron Lett.* **2000,** *41* (49), 9639-9643.
[186] Shotwell, J. B.; Koh, B.; Choi, H. W.; Wood, J. L.; Crews, C. M., Inhibitors of NF-κB signaling: design and synthesis of a biotinylated isopanepoxydone affinity reagent. *Bioorg. Med. Chem. Lett.* **2002,** *12* (23), 3463-3466.